Participation by consumer and interested persons in public hearing June 28, June 29, 2000 [Docket No. 00N-1256]; FDA Regulation of OTC Drug Products Hearing - RE: STATINS
(Pursuant to Federal Register/Vol. 65, No. 82/April 27, 2000 - part 15 hearing)

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Date of Presentation: June 29, 2000
Time: 10:40 am

00N-1256 TS 33

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EDUCATION

1996	**UCLA Law School; JD**
1988	**Pepperdine University; MBA**
1977	**Harvard Medical School;** Fellow in Ob. Gyn.
1976	**Harvard Medical School;** Fellow in Pediatric Medicine
1975	**Harvard Medical School; MD**
1971	**Brandeis University;** AB biology; Summa Cum Laude

PROFESSIONAL EXPERIENCE

1998-	**Partner, HEEGER & BARNETT, LLP,** Encino, CA
1996-1998	**Attorney, Law Offices of Bruce Barnett, M.D.,** Encino, CA
1/95-6/95	**Extern, United States Court of Appeals, Ninth Circuit, (Judge Harry Pregerson),** Woodland Hills, CA.
1994-1996	**Co-Founder, Medical Dynamics, Inc.** Los Angeles, CA
1979-93	**Founder and CEO, Full-Time Family Practice Physician, Family Medical Group, Family Medical Services, Inc.,** Van Nuys, CA.
1978-79	**Staff Emergency Room Physician,** Santa Teresita Hospital, Duarte, CA
1977-78	**Staff Emergency Room Physician,** Lynn Hospital., Lynn, MA.

CURRENT DIRECTORSHIPS

President, **Pasadena Young Musicians Orchestra**, Pasadena, CA

MEMBERSHIPS

Admitted to the Practice of Law by the State Bar of California
Admitted to Practice Law in U.S. Court of Appeals for the Ninth Circuit
Admitted to Practice Law in U.S. District Court, Central District
American Academy of Family Physicians, Fellow
American Bar Association
American Board of Quality Assurance, Diplomate
American College of Legal Medicine, Fellow, Diplomate
California Medical Association
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PULBICATIONS AND PRESENTATIONS - list available upon request

B

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April 3, 2000

John M. Sherman, Esq.
LAW OFFICES OF JOHN M. SHERMAN
116 North Maryland Avenue, Suite 240
Glendale, CA 91206-4263

DEATH SUMMARY

RE: CALABIO, Elnoisa (Deceased)
Empl: Kaiser Foundation Hospital
DOB: 03/17/51
SSN: 584-04-7744
WCAB No: VNO 0401 337
Claim No: 1000-00-0474
D/Death: 10/07/99

Dear Mr. Sherman:

This is a report pertaining to circumstances surrounding the death of Ms. Elnoisa Calabio, a former employee of Kaiser who died on October 7, 1999 at 48 years of age. Available for my review were copies of the following records. [I personally spent 4¾ hours reviewing the records, researching the medical literature and preparing this report.]

There was the report of a postmortem examination conducted on October 11, 1999 by Dr. R. Ridolfi, wherein he diagnosed Ms. Calabio with severe diffuse acute and chronic nonspecific interstitial pneumonitis, acute diffuse alveolar damage, bilateral pleural effusions and moderate nonspecific hepatic steatosis. There was no evidence for vasculitis or myositis.

In the summary of Ms. Calabio's history Dr. Ridolfi said that she had developed arthritic symptoms involving the fingers, wrists and knees in the summer of 1999, together with "dermatologic changes suggesting dermatomyositis." Then, she developed progressive shortness of breath and evidence for interstitial pneumonitis. She had been taking the medication Mevacor and this was discontinued. An open lung biopsy performed in September 1999 was interpreted at first as usual interstitial pneumonitis; later, the diagnosis was changed to nonspecific interstitial pneumonitis.

Dr. Ridolfi said that in the postmortem examination Ms. Calabio's skin and skeletal muscle revealed no signs of vasculitis or myositis. A special pathologic stain revealed evidence for interstitial fibrosis in the lungs.

There was the death certificate explaining that Ms. Calabio had died at 4:35 p.m. on October 7, 1999 at the Kaiser Hospital in West Los Angeles. The immediate cause of death was listed as "usual interstitial pneumonia" that had been present for days. This was attributed to dermatomyositis that had been present for two months.

There were records from the Kaiser Hospital showing that a bronchoscopy performed on August 18, 1999 was interpreted by the pathology department as showing "essentially non diagnostic lung parenchyma." A biopsy of the left thigh muscle performed on August 16, 1999 was interpreted as showing "unremarkable skeletal muscle tissue with no evidence of myositis or vasculitis."

The Kaiser records show that a biopsy of the stomach performed on August 9, 1999 revealed mild to moderate subacute and chronic gastritis with no signs of helicobacter. A biopsy of the skin on the left thigh performed on January 9, 1997 was interpreted as "cellular dermatofibroma." A stomach biopsy performed on December 28, 1994 revealed "mild chronic gastritis" with no evidence for H. pylori.

The Kaiser records show that a gallium scan of the lungs performed on August 17, 1999 was normal. An open lung biopsy performed on September 15, 1999 was initially interpreted as usual interstitial pneumonia, with no evidence for granuloma or vasculitis. However, the pathology specimen was then reviewed by a pathologist at USC Medical Center who interpreted this as "nonspecific interstitial pneumonitis...fibrosing and cellular type."

The Kaiser records include the September 26, 1999 pathology consultation by Dr. M. Koss at USC Medical Center, explaining that Ms. Calabio had developed progressive shortness of breath beginning shortly after taking the medication Zocor. He diagnosed her with nonspecific interstitial pneumonitis (NSIP), adding "this pattern of lung injury is typically chronic and includes a wide variety of illnesses. The idiopathic form of the disease, when it shows fibrosis, as in the present case, has a prognosis somewhat better than that of [usual interstitial fibrosis], but it can progress to end-stage lung disease as apparently has happened here. I am not aware of a relation of NSIP to Zocor."

The Kaiser records include a scientific article by Katzenstein and Fiorelli (published in the 1994 *American Journal of Surgical Pathology*, Volume 18, beginning on page 136) entitled "Nonspecific Interstitial Pneumonia/Fibrosis." This article was reviewed in detail and explained that the mortality of nonspecific interstitial pneumonitis was less than that of usual interstitial pneumonitis. Some patients described in this article had a history of exposure to substances at work or at home that might have caused the pneumonia, such as a canary, a wood stove, grain dust, coal or ash.

The Kaiser records show that Ms. Calabio was admitted to the hospital on August 28, 1997 with a two-day history of chest pains and tingling sensations in her left arm. At that time it was said that she had a history of hypertension and hypercholesterolemia and was taking the medication Maxzide. On physical examination her blood pressure was 159/77 and she was diagnosed with atypical chest pain. She was admitted for further evaluation.

The Kaiser records show that on October 31, 1996 Ms. Calabio underwent vaginal hysterectomy surgery for uterine fibroids. In her preoperative evaluation it was said that she had a history of headache and "sinus pain," and was on the medication Maxzide for hypertension. Her blood pressure was 120/70.

The Kaiser records include a September 14, 1992 health questionnaire wherein Ms. Calabio acknowledged a history of hay fever in the past and a more recent history of "allergies." On January 25, 1993 she weighed 120 pounds and her blood pressure was 128/86. On July 27, 1993 she underwent injection of cortisone into her right thumb to correct trigger thumb.

The Kaiser records show that Ms. Calabio underwent esophagogastroduodenoscopy (EGD) on December 28, 1994 because of a history of epigastric and right upper quadrant discomfort. She was diagnosed with duodenitis and mild gastritis. On March 23, 1995 Ms. Calabio was evaluated for chest pains and high blood pressure. Her only medication at that time was Tagamet. Her blood pressure ranged from 160/110 to 170/110.

Ms. Calabio was told to return the following week for a blood pressure check. On April 7, 1995 her blood pressure was 150/90 and she weighed 134 pounds. She was diagnosed with "mild" hypertension and hypercholesterolemia. (I don't believe medication was prescribed at that time for her blood pressure, however.)

The Kaiser records show that on August 21, 1995 Ms. Calabio complained of the sudden onset of rectal pain while standing and writing on the operating room schedule board that evening. She was diagnosed with no anal pathology but a vaginal infection was present. In a May 22, 1996 health questionnaire it was said that Ms. Calabio had a history of a positive PPD skin test. On August 28, 1997 it was said that she had a two-day history of intermittent chest pressure and her blood pressure was 159/77. She was diagnosed with atypical chest pains. (She was admitted to the hospital for evaluation at that time.)

The Kaiser records show that on September 10, 1997 it was said that Ms. Calabio possibly had a history of esophageal spasm or esophagitis secondary to gastroesophageal reflux disease (to explain her recent bout of atypical chest pains, that is). She weighed 130 pounds and her blood pressure was 151/78. On April 21, 1998 she was diagnosed with a right shoulder impingement syndrome and arthritis changes in her neck. Physical therapy was recommended.

The Kaiser records show that on March 26, 1999 Ms. Calabio complained of recurrent epigastric pain for which she had been taking Tagamet and Mylanta. She was taking the medication Maxzide. Prilosec was prescribed. On April 20, 1999 it was said that Ms. Calabio's total cholesterol was 276, the HDL was 46, the LDL was 158 and the triglycerides were 378. On July 28, 1999 it was said that Ms. Calabio had a history of left knee pain and swelling for several days and had taken the medication Motrin. A mild to moderate left knee effusion was present and the knee was tapped and fluid was sent to the laboratory for testing. No injection was made, however.

The Kaiser records show that on August 3, 1999 it was said that Ms. Calabio had developed muscle weakness, nausea, arthralgias and myalgias after starting the medication Zocor at a dose of 40 mg at nighttime on July 14, 1999. There was also a rash on her face, knuckles and elbows. Laboratory tests included a total CPK that was slightly elevated at 283. The SGOT was slightly elevated at 58. She was diagnosed with dermatomyositis secondary to Zocor (which had already been discontinued), and the medication Prednisone was prescribed. Also, Ms. Calabio was started on Cytotec.

The Kaiser records show that on August 9, 1999 it was said that Ms. Calabio only took the Prednisone for two days because it upset her stomach. On physical examination her heart and lungs were normal. She was diagnosed with possible "Zocor reaction." On August 9, 1999 her EGD revealed multiple erosions in the stomach.

The Kaiser records include the August 13, 1999 consultation by a neurologist, Dr. K. Kim, wherein it was said that Ms. Calabio took Zocor for about one week until July 24, 1999. While taking this medication she developed a rash on her face, arthritis in the small joints, arthralgias and oral ulcers. He diagnosed her with no evidence for neuromuscular pathology; rather, Dr. Kim concluded that Ms. Calabio had "probable allergic reaction to Zocor and delayed reaction."

The Kaiser records show that Ms. Calabio had been admitted to the hospital from August 13, 1999 to August 19, 1999 in order to evaluate her nausea, weakness and fatigue that had been present for several weeks. Bronchoscopy was accomplished but was negative. A gallium scan was normal. She was diagnosed with dermatomyositis "probably related to Zocor with lung involvement," transient congestive heart failure, hypertension, hypercholesterolemia and "gastric ulcers."

The Kaiser records show that Ms. Calabio was admitted from September 4, 1999 to September 5, 1999 after a fainting spell that occurred when she got out of bed. She was diagnosed with medication-induced hypotension. Also, doctors diagnosed "dermatomyositis secondary to Zocor reaction."

The Kaiser records include the October 4, 1999 consultation by Dr. T. Mahrer. This was a lung transplant evaluation wherein it was said that Ms. Calabio's condition had progressed to require intubation for ventilatory assist on October 2, 1999. Her condition had deteriorated further. She had developed a fever too. A recent echocardiogram had revealed no evidence for significant pulmonary hypertension. Dr. Mahrer did not believe that a living related lung transplant would be appropriate treatment for Ms. Calabio. He made recommendations for improving her oxygenation.

These were the only records available for me to review at this time.

DISCUSSION:

I was asked to describe circumstances surrounding the death of Ms. Elnoisa Calabio, a former employee of Kaiser who died on October 7, 1999 at 48 years of age. Based on the available information, this woman's work as an operating room nurse did not cause, aggravate or accelerate her demise.

At the time of her death Ms. Calabio's medical problems included: hypercholesterolemia; history of hypertension diagnosed in 1995; history of gastritis confirmed on biopsies in December 1994 and August 1999; history of right shoulder impingement syndrome; history of atypical chest pains in 1997, suspected to be the result of gastrointestinal disease (i.e., gastritis or gastroesophageal reflux); left knee arthritis diagnosed in July 1999; polyarthralgia and malaise beginning within one week of starting the medication Zocor in July 1999; nonspecific interstitial pneumonitis diagnosed in September 1999, resulting in respiratory failure and death the following month.

The preponderance of evidence indicates that Ms. Calabio's demise was directly precipitated by consumption of a new medication (new to her, that is) last July. On or about July 14, 1999 she was given the medication Zocor for hypercholesterolemia. Within one week of taking the medication she experienced malaise, arthralgias and a left knee joint effusion, and she discontinued the drug altogether on or about July 24, 1999. Her problems did not end there, however, and Ms. Calabio eventually developed signs and symptoms of progressive pulmonary disease that was ultimately diagnosed as nonspecific interstitial pneumonitis.

The medication Zocor has been reported to cause malaise, arthralgias, arthritis, vasculitis-like symptoms, dyspnea and fatty changes in the liver. All of these things occurred in Ms. Calabio's case. (As seen in the postmortem examination, the pathologist observed moderate steatosis, fatty changes in Ms. Calabio's liver.) There was nothing about her work environment that could have caused, aggravated or accelerated this condition, based on the information at hand.

Therefore, the preponderance of evidence indicates that Ms. Elnoisa Calabio's death from nonspecific interstitial pneumonitis was not caused, aggravated or in any way accelerated by her employment at Kaiser. This is simply not the history of an occupational death; rather, it is a sad reminder of the potential consequences of properly prescribed prescription medications.

As always, however, I would be happy to review any additional medical records that become available on this case in order to provide a more thorough discussion of Ms. Elnoisa Calabio's entire past medical history.

Sincerely,

Timothy C. Reynolds, MD

TIMOTHY C. REYNOLDS, M.D.
Diplomate, American Board of Internal Medicine

April 3, 2000

TCR:kdg

cc: Paul Majchrowicz, Kaiser Permanente

I declare under penalty of perjury that the information contained in this report and its attachments, if any, is true and correct to the best of my knowledge and belief, except as to information I have indicated I have received from others. As to that information, I declare under penalty of perjury that the information accurately describes the information provided to me and, except as noted herein, that I believe it to be true.

I also declare under penalty of perjury that I have not violated Labor Code Section 139.3 and that I have not offered, delivered, received or accepted any rebate, refund, commission, preference, patronage, dividend, discount or other consideration, whether in the form of money or otherwise, as compensation or inducement for any referred examination or evaluation. The contents of this report are true and correct to the best knowledge of the undersigned.

I declare under penalty of perjury that the above is true and correct.

This was executed in the County of Los Angeles on

4/5/2000 *by* T C Reynolds, MD

TIMOTHY C. REYNOLDS, M.D.
A Medical Corporation

LAW OFFICES OF JOHN M. SHERMAN

JOHN M. SHERMAN, ESQ.

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April 20, 2000

WORKERS COMPENSATION APPEALS BOARD
6150 Van Nuys Boulevard
Room 105
Van Nuys, CA. 91401-3373

RE: ELNOISA CALABIO (DEC'D.) VS. KAISER FOUNDATION HOSPITAL
WCAB NO. : VNO 0401 337
CLAIM NO. : 1000-00-0474
D.O.I. : 10/7/99
FACILITY : West Los Angeles Medical Center

Gentlepersons:

Pursuant to the Rules of Practice and procedure enclosed please find the following documents for filing:

1. **Timothy Reynolds, M.D., dated 4/3/00.**

Copies of the above have been served on the parties listed below.

Very truly yours,

LAW OFFICES OF JOHN M. SHERMAN
Attorneys at Law

By: JOHN M. SHERMAN, ESQ.

JMS:ems

Enclosure

cc: Kaiser Permanente Medical Care Program/Paul Majchrowicz
Law Offices of Appel & Rimbach/Barry M. Appel, Esq.

C

ENTERTAINMENT

ZOCOR®
(SIMVASTATIN)

PLEASE READ THIS SUMMARY CAREFULLY, AND THEN ASK YOUR DOCTOR ABOUT ZOCOR. NO ADVERTISEMENT CAN PROVIDE ALL THE INFORMATION NEEDED TO PRESCRIBE A DRUG. THIS ADVERTISEMENT DOES NOT TAKE THE PLACE OF CAREFUL DISCUSSIONS WITH YOUR DOCTOR. ONLY YOUR DOCTOR HAS THE TRAINING TO WEIGH THE RISKS AND BENEFITS OF A PRESCRIPTION DRUG FOR YOU.

USES OF ZOCOR

ZOCOR is a prescription drug that is indicated as an addition to diet for many patients with high cholesterol when diet and exercise are inadequate. For patients with coronary heart disease (CHD) and high cholesterol, ZOCOR is indicated as an addition to diet to reduce the risk of death *by reducing coronary death; to reduce the risk of heart attack; to reduce the risk for undergoing* cardiac procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty); and to reduce the risk of stroke or transient ischemic attack (TIA).

WHEN ZOCOR SHOULD NOT BE USED

Some people should not take ZOCOR. Discuss this with your doctor.

ZOCOR should not be used by patients who are allergic to any of its ingredients. In addition to the active ingredient simvastatin, each tablet contains the following inactive ingredients: *cellulose, lactose, magnesium stearate, iron oxides, talc, titanium dioxide, and starch. Butylated* hydroxyanisole is added as a preservative.

Patients with liver problems: *ZOCOR should not be used by patients with active liver disease or* repeated blood test results indicating possible liver problems. (See WARNINGS.)

Women who are or may become pregnant: Pregnant women should not take ZOCOR because it may harm the fetus. **Women of childbearing age should not take ZOCOR unless it is highly unlikely that they will become pregnant.** If a woman does become pregnant while on ZOCOR *she should stop taking the drug and talk to her doctor at once.*

Women who are breast-feeding should not take ZOCOR.

WARNINGS

Muscle: Tell your doctor right away if you experience any unexplained muscle pain, tenderness, or weakness at any time during treatment with ZOCOR so your doctor can decide if ZOCOR should be stopped. Some patients may have muscle pain or weakness while taking ZOCOR. Rarely, this can include muscle breakdown resulting in kidney damage. The risk of muscle breakdown is greater in patients taking certain other drugs along with ZOCOR, such as the lipid-lowering drug Lopid (gemfibrozil), and other fibrates; lipid-lowering doses of niacin (*nicotinic acid*); Sandimmune (cyclosporine); *itraconazole*, ketoconazole, *and other* azole antifungal drugs; the antibiotics erythromycin and clarithromycin; HIV protease inhibitors; and the antidepressant nefazodone. Interruption of therapy with ZOCOR should be considered if you are going to take an azole antifungal medication, such as itraconazole, or macrolide antibiotics, such as erythromycin. Patients using ZOCOR along with any of these *other drugs should be carefully monitored by their physician. The risk of muscle breakdown* is greater in patients with kidney problems or diabetes.

Because there are risks in combining therapy with ZOCOR with the drugs listed above, *your* doctor should carefully weigh the potential benefits and risks. He or she should also carefully monitor patients for any muscle pain, tenderness, or weakness, particularly during the initial months of therapy and if the dose of either drug is increased. Your doctor also may monitor the level of certain muscle enzymes in your body, but there is no assurance that such *monitoring will prevent the occurrence of severe muscle disease.*

If you have conditions that can increase your risk of muscle breakdown, which in turn can cause kidney damage, your doctor should temporarily withhold or stop ZOCOR. Also, since there are no known adverse consequences of briefly stopping therapy with ZOCOR, treatment should be stopped a few days before elective major surgery and when any major acute medical or surgical condition occurs. Discuss this with your doctor, who can explain these conditions to you.

Liver: About 1% of patients who took ZOCOR in clinical trials developed elevated levels of some liver enzymes: Patients who had these increases usually had no symptoms. Elevated liver *enzymes usually returned to normal levels when therapy with ZOCOR was stopped.*

In the ZOCOR Survival Study, the number of patients with more than one liver enzyme level elevation to greater than 3 times the normal upper limit was no different between the ZOCOR and placebo groups. Only 8 patients on ZOCOR and 5 on placebo discontinued therapy due to elevated liver enzyme levels. Patients were started on 20 mg of ZOCOR, and one third had their dose raised to 40 mg.

Your doctor should perform routine blood tests to check these enzymes before you start treatment with ZOCOR and periodically thereafter (for example, semiannually) for your first year of treatment or until 1 year after your last elevation in dose. Patients titrated to the 80-mg dose should receive an additional test at 3 months. If your enzyme levels increase, your doctor should order more frequent tests. If your liver enzyme levels remain unusually high, your doctor should discontinue your medication.

Tell your doctor about any liver disease you may have had in the past and about how much alcohol you consume. *ZOCOR should be used with caution in patients who consume large amounts of alcohol.*

PRECAUTIONS

Before starting treatment with ZOCOR, try to lower your cholesterol by other methods such as diet, exercise, and weight loss. Ask your doctor about how best to do this. Any other medical problems that can cause high cholesterol should also be treated.

Drug Interactions: Because of possible serious drug interactions, it is important to tell your doctor what other drugs you are taking, including those obtained without a prescription.

ZOCOR *can interact with cyclosporine (Sandimmune), itraconazole, ketoconazole, Lopid, niacin,* erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone. (See WARNINGS, Muscle.)

Some patients taking lipid-lowering agents similar to ZOCOR and coumarin anticoagulants (a type of blood thinner) have experienced bleeding and/or increased blood clotting time. Patients taking these medicines should have their blood tested before starting therapy with ZOCOR and should continue to be monitored.

Central Nervous System Toxicity; Cancer, Mutations, Impairment of Fertility: Like most prescription drugs, ZOCOR was required to be tested on animals before it was marketed for human use. Often these tests were designed to achieve higher drug concentrations than humans achieve at recommended dosing. In some tests, the animals had damage to the nerves in the central nervous system. In studies of mice with high doses of ZOCOR, the likelihood of certain types of cancerous tumors increased. No evidence of mutations of or damage to genetic material has been seen. In one study with ZOCOR, there was decreased fertility in male rats.

Pregnancy: Pregnant women should not take ZOCOR because it may harm the fetus.

Safety in pregnancy has not been established. In studies with lipid-lowering agents similar to ZOCOR, there have been rare reports of birth defects of the skeleton and digestive system. Therefore, women of childbearing age should not take ZOCOR unless it is highly unlikely they will become pregnant. If a woman does become pregnant while taking ZOCOR, she should stop taking the drug and talk to her doctor at once. The active ingredient of ZOCOR did not cause birth defects in rats at 3 times the human dose or in rabbits at 3 times the human dose.

Nursing Mothers: Drugs taken by nursing mothers may be present in their breast milk. Because of the potential for serious adverse reactions in nursing infants, a woman taking ZOCOR should not breast-feed. (See WHEN ZOCOR SHOULD NOT BE USED.)

Pediatric Use: ZOCOR is not recommended for children or patients under 20 years of age.

THE WALL STREET JOURNAL FRIDAY, JANUARY 28, 2000 W9W

SIDE EFFECTS

Most patients tolerate treatment with ZOCOR well; however, like all prescription drugs, ZOCOR can cause side effects, and some of them can be serious. Side effects that do occur are usually mild and short-lived. Only your doctor can weigh the risks versus the benefits of any prescription drug. *In clinical studies with ZOCOR, less than 1.5% of patients dropped out of the studies* because of side effects. In a large, long-term study, patients taking ZOCOR experienced similar side effects to those patients taking placebo (sugar pills). Some of the side effects that have been reported with ZOCOR or related drugs are listed below. This list is not complete. Be sure to ask your doctor about side effects before taking ZOCOR and to discuss any side effects that occur.

Digestive System: Constipation, diarrhea, upset stomach, gas, heartburn, stomach pain/cramps, anorexia, loss of appetite, nausea, inflammation of the pancreas, hepatitis, jaundice, fatty changes in the liver, and rarely, severe liver damage and failure, cirrhosis, and liver cancer.

Muscle, Skeletal: Muscle cramps, aches, pain, and weakness; joint pain; muscle breakdown.

Nervous System: Dizziness, headache, insomnia, tingling, memory loss, damage to nerves causing weakness and/or loss of sensation and/or abnormal sensations, anxiety, depression, tremor, loss of balance, psychic disturbances.

Skin: Rash, itching, hair loss, dryness, nodules, discoloration.

Eye/Senses: *Blurred vision, altered taste sensation, progression of cataracts, eye muscle* weakness.

Hypersensitivity (Allergic) Reactions: On rare occasions, a wide variety of symptoms have been reported to occur either alone or together in groups (referred to as a syndrome) that appeared to be based ~~on~~ allergic-type reactions, which may rarely be fatal. These have included *one or more of the following: a severe generalized reaction that may include shortness of breath,* wheezing, digestive symptoms, and low blood pressure and even shock; an allergic reaction with swelling of the face, lips, tongue and/or throat with difficulty swallowing or breathing; symptoms mimicking *lupus (a disorder in which a person's immune system may attack parts of* his or her own body); severe muscle and blood vessel inflammation; bruises; various disorders of blood cells (that could result in anemia, infection, or blood clotting problems) or abnormal blood tests; inflamed or painful joints; hives; fatigue and weakness; sensitivity to sunlight; fever, chills; flushing; difficulty breathing; and severe skin disorders that vary from rash to a serious burn-like shedding of skin all over the body, including mucous membranes such as the lining of the mouth.

Other: Loss of sexual desire, breast enlargement, impotence.

Laboratory Tests: Liver function test abnormalities including elevated alkaline phosphatase and bilirubin; thyroid function abnormalities.

NOTE: This summary provides important information about ZOCOR. If you would like more information, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them.

ZOCOR is a registered trademark of Merck & Co., Inc.

The other brands listed are trademarks of their respective owners and not of Merck & Co., Inc.

MERCK
Whitehouse Station, NJ 08889

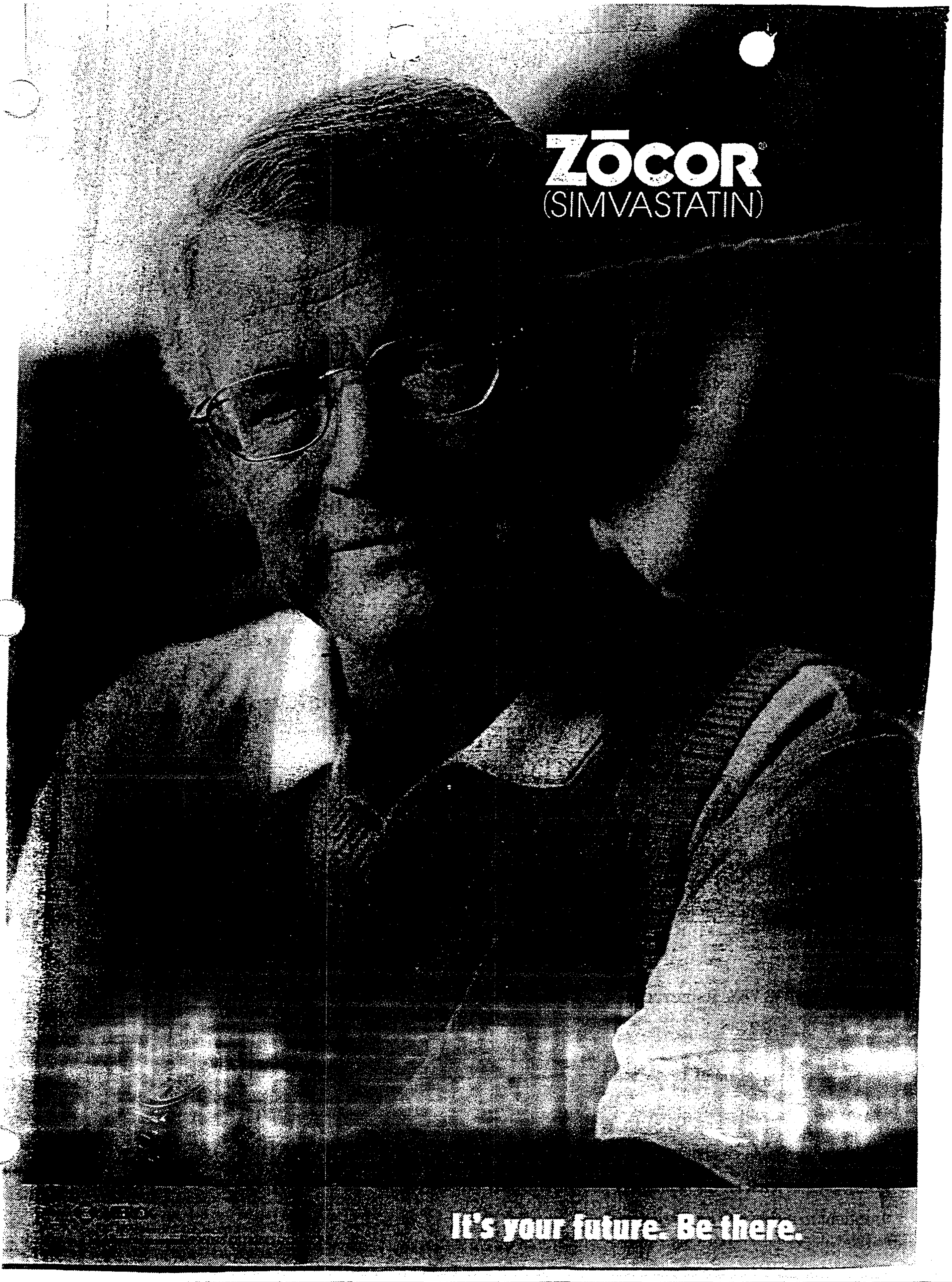
 996096(5)(435C)-ZOC-CON (435R)C

Suddenly, lowering my high cholesterol became even more important than football.

–Head Coach Dan Reeves

Only six weeks before one of the most important games of my life, I felt a strange pain in my chest – and wanted to ignore it. I mentioned it to my doctor, who encouraged me to get it checked out the next day. What they found was unlike any opponent I had ever faced: three of my arteries were more than 90 percent blocked. I was suffering from heart disease and had to undergo emergency bypass surgery. Fortunately, I had a full recovery, and was even able to coach my team in the biggest game of the season four weeks later. Looking back, I wish I had done some of the things I am doing now to take better care of myself. Some of those things include a better diet, regular exercise, and taking ZOCOR to help significantly lower my total cholesterol. When diet and exercise are not enough, ZOCOR can help people with high cholesterol and heart disease live a longer life by reducing the risk of a heart attack. ZOCOR is a prescription medication, so you should ask your doctor or healthcare professional if ZOCOR is right for you. ZOCOR isn't for everyone, including women who are pregnant or nursing or who may become pregnant, people who are allergic to any of its ingredients, or anyone with liver disease. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect and should be reported to your doctor right away. Your doctor may do simple blood tests before and during treatment with ZOCOR to check for liver problems. Be sure your doctor knows about medications you may be taking in order to avoid any serious drug interactions. With so much to look forward to, don't let high cholesterol and heart disease take you out of the game.

YOUR RESULTS MAY VARY.
PLEASE READ THE ADDITIONAL INFORMATION ON ZOCOR IMMEDIATELY FOLLOWING THIS AD.


ZOCOR®
(SIMVASTATIN)
It's your future. Be there.

D

British J. Rheum. Vol 33, p.—

Calabio

Simvastatin-associated Dermatomyositis

SIR—We read with interest the article by McDonagh *et al.* [1] and would like to report the following case. Recently we have seen a 50-yr-old man who was started on simvastatin [3-hydroxy-3-methyl glutaryl co. enzyme-A (HMG-COA) reductase inhibitor] in February 1990. Six months later he developed a non-itchy rash on the dorsum of his hands followed within a few months by proximal muscle weakness. Simvastatin was stopped in July 1992 by his general practitioner but he continued to have the symptoms. On presentation in December 1992 he had a rash entirely characteristic of dermatomyositis with papular, purplish erythema and scaling primarily on knuckles and nail folds with streaking along the extensor tendons of proximal phalanges and some nail fold telangiectasiae. He also had a non-specific rash on his elbows and face and he had evidence of proximal muscle weakness. The investigations showed creatinine kinase raised at 1045 units, (normal range 25–190), electromyogram revealed myopathic motor units and muscle biopsy showed patchy lymphocytic infiltration with muscle fibre degeneration in keeping with subacute myositis. His ANF was positive at 1/250 IgG. Investigation for an underlying neoplasm was negative. He was started on prednisolone which has been gradually tapered and 5 months later he has greatly improved and the rash has completely resolved.

HMG-COA reductase inhibitors are used for the treatment of familial hypercholesterolaemia. Transient rises in serum creatinine kinase are common and cases of myopathy and rhabdomyolysis [2–5] have been reported with the use of these drugs. There has been one reported case of dermatomyositis syndrome [6] developing in a patient on pravastatin (HMG-COA reductase inhibitor) therapy, however the skin lesions described were bullous and erythematous involving face, neck, shoulders and chest and were not typical of dermatomyositis.

To our knowledge this is the first reported case of classical dermatomyositis developing in a patient on simvastatin therapy. Although a direct casual link has not been established here, and the positive ANA and persistence of the rash long after stopping simvastatin may point to an immunological mechanism, we feel that clinicians should be aware of the possibility that this type of drug may provoke dermatomyositis.

F. H. KHATTAK,* I. M. MORRIS,* W. A. BRANFORD†
*Departments of *Rheumatology and †Dermatology, Kettering General Hospital, Rothwell Road, Kettering, Northants NN16 8UZ*
Accepted 28 October 1993

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'Inflammation or Sepsis' is not the Actual Question in Reactive Arthritis

SIR—In their recent editorial Highton and Poole [1] suggest that differences in the characteristics of patients studied as well as technical factors are most likely to be responsible for the variable detectability of *Chlamydia trachomatis* DNA and RNA in patients with sexually acquired reactive arthritis (SARA). In fact two additional investigations not cited in the editorial have identified chlamydial nucleic acids, especially ribosomal RNA in joint material of patients, with *Chlamydia*-induced arthritis (CIA) and undifferentiated arthritis, and DNA encoding for the chlamydial major outer-membrane protein (MOMP) in joint material of patients with SARA [2, 3]. Therefore, we agree with the conclusion that live organisms are disseminated to the affected joints, but it is questionable if the intra-articular presence of *C. trachomatis* represents a productive infection. We have established an *in vitro* model of *C. trachomatis* (serovar K)-infected monocytes [4]. Chlamydial MOMP, lipopolysaccharide and ribosomal RNA persist in these infected monocytes without productive infection for up to 14 days. Similar findings were reported in a primate model for trachoma, in which chlamydial RNA and DNA could be demonstrated during a culture-negative state [5]. Attempts to culture replicating *Chlamydiae* reproduceably from joint materials by modern cell culture techniques have failed [6]. The electron-microscopic studies showing particles consistent with both elementary and reticulate bodies are not definite proof of a replicative infection. Therefore, future investigations on the pathomechanisms of intra-articular persistence of *C. trachomatis* should include the issue of a culture-negative state of persistence and growth arrest of the bacterial organism.

The authors further refer to data showing the presence of antigenic material or lipopolysaccharide from *Yersinia* and *Salmonella* within the joints of patients with reactive arthritis following enteric infection (EReA). We demonstrated *Yersinia* outer-membrane-protein (YadA)-positive structures resembling rod-shaped bacteria in biopsies of the synovial membrane in patients with *Yersinia*-induced arthritis (YIA) [7]. Granfors and colleagues [8] also described rod-shaped particles in SF cells of one patient with YIA pointing to the presence of whole micro-organisms in affected joints. Moreover, the dissemination of whole *Yersiniae* to lymph nodes, skin and liver has been shown in patients with other extraintestinal inflammatory complications of chronic *Yersinia* infections [9]. With regard to YIA it seems to be too early to conclude the definitive absence of nucleic acids or live *Yersiniae* in inflamed joints based on two reports with negative PCR results. One of these reports was further discussed because of potential errors in interpretation [10]. As in CIA further studies with different molecular methods may be needed to identify nuclear acids in joints of patients with EReA.

In conclusion, the question 'inflammation or sepsis' is not the exact issue of the pathogenesis of infection in reactive arthritis. Dumonde classified the association of arthritis and infection into four classes: infective, post-infective, reactive, and inflammatory [11]. According to this classification reactive arthritis is neither 'inflammatory' or 'infective' (i.e. 'septic'), but rather 'post-infective', because bacterial antigens, nucleic acids, and presumably live bacteria can be identified in joint material without positive culture of micro-organisms as in true 'septic' arthritis. The original description of 'reactive' arthritis as an acute non-purulent arthritis complicating an infection elsewhere in the body without intra-articular presence of bacterial components is not true for SARA and EReA [12]. The experience of reactive arthritis, Lyme arthritis and per-

Dermatomyositis with lung involvement in a patient treated with simvastatin

Simvastatin is widely used in the treatment of hypercholesterolaemia. We report the case of a 76-year-old woman, receiving long term simvastatin therapy, who developed dermatomyositis with lung involvement, resulting in a fatal outcome.

She presented to her general practitioner with a two week history of rash, proximal limb weakness and dyspnoea on exertion. Simvastatin 10mg daily, which she had been receiving for 18 months for a cholesterol level of 6.3 U/L (normal range <5.5 U/L), was immediately ceased. Laboratory examination revealed an elevated creatinine kinase (CK) level of 1246 U/L (range 80-190 U/L). Despite the subsequent fall in CK level to the normal range, proximal limb weakness worsened. Examination revealed an erythematous rash involving trunk, arms and proximal lower limbs, associated with subcutaneous oedema, most marked in the arms. There was mild weakness of the proximal limb musculature and bibasal inspiratory crackles.

Laboratory examination revealed a positive antinuclear antibody at a titre of 1:2560 of speckled pattern; extractable nuclear antigen testing (including Jo-1) was negative. Other anti-synthetase autoantibodies were not tested. Erythrocyte sedimentation rate was 60 mm/hr. Her HLA Class II tissue type was HLA-DR3, 4, w52, w53

Open muscle biopsy of the right quadriceps muscle was non-diagnostic, revealing non-specific type IIb muscle atrophy and vacuolar changes. A high resolution computerised tomography of chest revealed extensive alveolar infiltrates in both lungs, predominantly at the bases. Transbronchial biopsy yielded tissue with interstitial inflammation and early fibrotic changes.

Due to deteriorating lung function, she was commenced on high dose oral corticosteroid. Despite the resolution of her rash and improvement in her muscle strength, respiratory function continued to worsen over the next ten days. She was admitted to the intensive care unit for ventilatory support and oral cyclophosphamide was commenced. Open lung biopsy revealed new and old fibrosis with diffuse alveolar damage. In view of the irreversible nature of the damage, ventilatory support was withdrawn 12 weeks after initial presentation to her local doctor.

Post-mortem examination revealed interstitial pulmonary fibrosis with smaller areas consistent with aspiration pneumonia and bronchiolitis obliterans organising pneumonia. Myositis with severely atrophic myocytes and focal lymphocyte collections was present in proximal muscle (Figure 1).

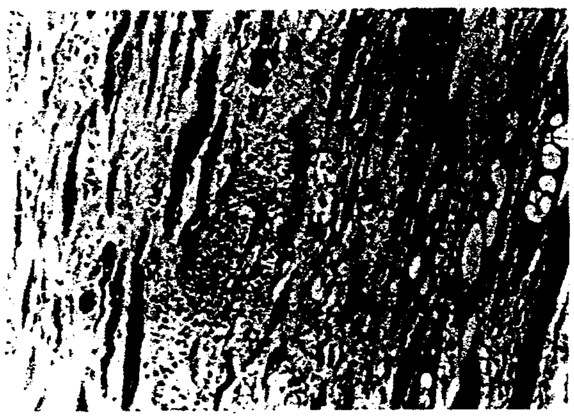

Figure 1: Specimen of quadriceps muscle taken at post-mortem. Prominent vacuolation of muscle fibres, degeneration and atrophy with replacement fibrosis, lymphocytic infiltration and cluster of large vesicular nuclei (arrow). Haematoxylin and eosin; original magnification 200x.

Simvastatin, like other HMG-Co A reductase inhibitors, is associated with muscular side effects including asymptomatic CK elevations (0.6%), non-inflammatory myopathy (0.01%-0.08%) and several reports of rhabdomyolysis.[1,2] In addition, there are two case reports of an inflammatory myopathy.[3,4] Both cases resolved completely with cessation of the drug, with no lung involvement or residual morbidity.[3,4] The mechanism of muscle toxicity remains unclear, although it has been speculated that reduced levels of mevalonic acid caused by HMG-CoA reductase inhibition can cause muscle damage.[5]

The temporal association of our patient's illness with simvastatin, together with the return of elevated CK levels to normal on cessation of the drug, suggest a simvastatin related adverse reaction. The mechanism of this reaction is unclear. Our patient had the HLA-DR3 genotype which has been associated with polymyositis and Jo-1 autoantibodies,[6] and her sister died of idiopathic pulmonary fibrosis. Simvastatin may have triggered an autoimmune dermatomyositis by producing muscle injury and releasing autoantigens, or by acting as a hapten to produce a new antigen, however, this is purely speculative.

The use of cholesterol lowering agents for the secondary prevention of vascular disease has shown established mortality benefit for some groups.

However, the benefit of treating an elderly female with asymptomatic hypercholesterolaemia has not been shown. This case highlights the need for enthusiasm for preventive therapy to be tempered by the recognition of the risks of adverse events. ■

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Angio-oedema and ACE inhibitors

We were interested to read Dr Weiner's report on angio-oedema due to angiotensin converting enzyme inhibitors (ACEIs).[1] We have also seen a number of patients who have had repeated episodes of angio-oedema associated with ACE inhibitors. One woman had suffered from three or four attacks of angio-oedema a year before she started treatment with lisinopril. She documented 42 attacks over the next 12 months before the lisinopril was stopped. These episodes involved the tongue, lips and eyes but none were life threatening.

ACE inhibitors can also potentiate the response to bee or wasp venom. There are reports of patients who developed anaphylactic reactions during desensitisation with wasp venom while taking ACE inhibitors. The desensitisation was completed uneventfully once the enalapril was discontinued.[2] We have seen one woman who had generalised angio-oedema in response to bee stings on at least three occasions, over the course of four years, while taking first captopril and then cilazapril. Prior to taking ACE inhibitors and since discontinuing them she has only had localised swelling at the site of bee stings.

Stopping ACE inhibitors because of angio-oedema can also cause considerable problems in patients with severe congestive heart failure. We have seen two such patients. One patient had 12 episodes of angio-oedema and another three episodes of angio-oedema while taking ACE inhibitors. Both patients had potentially life threatening attacks with laryngeal oedema and required treatment with adrenaline. In both instances the heart failure became very difficult to treat after the ACE inhibitor was discontinued and the patients have had repeated hospital admissions for heart failure. In one instance we have recommenced captopril at the request of the patient and his family. We hope that this is an interim measure until we can obtain supplies of losartan. Losartan is an Angiotensin II receptor antagonist which is already registered in a number of countries.[3] Because it does not inhibit the breakdown of bradykinin we hope that it will not cause angio-oedema in this individual. ■

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The recent article by Weiner on angio-oedema in association with angiotensin converting enzyme inhibitors (ACEIs) was a timely reminder that this adverse reaction is a class effect of ACEIs and that the reaction may not always occur soon after the drug is commenced.[1] The Adverse Drug Reactions Advisory Committee (ADRAC) has received a total of 182

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Interstitial lung disease with pleural effusion caused by Simvastin

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Abstract. De Groot REB, Willems LNA, Dijkman JH (Department of Pulmonology, Leiden University Hospital, Leiden, The Netherlands). Interstitial lung disease with pleural effusion caused by Simvastin (Case Report). *J. Intern Med* 1996; 239: 361–3.

Simvastin, a HMG-CoA reductase blocker, is used for the treatment of certain forms of hypercholesterolaemia. Simvastin is prescribed to lower high serum levels of cholesterol by inhibiting a specific enzyme, hydroxy-methylglutarylCo-enzym-A (HMG-CoA) reductase. This ultimately leads to an increase of the number of LDL-receptors in the liver, and thus, to a decrease of the serum LDL-cholesterol. To a much lesser extent it lowers the serum VLDL-cholesterol and makes the serum HDL-cholesterol level rise. In general, this relatively new compound is well tolerated and only a few, mostly minor, adverse effects have been reported so far. We present a patient who developed interstitial lung disease with pleural effusion most probably as a result of the use of Simvastin.

Keywords: adverse effect, interstitial lung disease, pleural effusion, simvastin.

Case report

A 61-year-old male was referred to our outpatient clinic. Several years before, he had survived five myocardial infarctions before being subjected to coronary bypass surgery. At the time of his first visit to our clinic, he had a non-productive cough and dyspnea with fatigue for 6 weeks. Later, there were small amounts of viscous white sputum which were bloodstained only once. There was no evidence of cardiac failure. He had no history of chronic cough or sputum production despite the fact that he had a 31 pack-years smoking history. There was no weight loss, joint or muscle pain. He did not keep pigeons or other birds, nor did he keep any other domestic animals. He had retired 2.5 years previously. Until then, he was employed in an archive. He had taken isosorbidedinitrate, fenprocoumon and diltiazem for several years, to which Simvastin 10 mg daily had been added 6 months earlier.

Physical examination revealed dyspnea at rest and a respiratory frequency of more than 40 breaths per minute. There was no cyanosis and no lymphadenopathy. Examination of the thorax showed bilateral crackles heard over the lower lungfields. His fingers showed minor signs of clubbing. X-ray examination of the chest at that time showed an interstitial lung disease and pleural effusion that had not been present before.

Laboratory examination showed the following data: ESR 37 mm, haemoglobin 8.1 mmol L^{-1}, haematocrit 40, WBC $12.7 \times 10^9 L^{-1}$, with 70% neutrophils, 22% lymphocytes and 1.5% eosinophils, thrombocyte count $476 \times 10^9 L^{-1}$, serum urea, creatinine and electrolytes were normal. Transaminases were severely elevated, ASAT 740 UL^{-1} (N

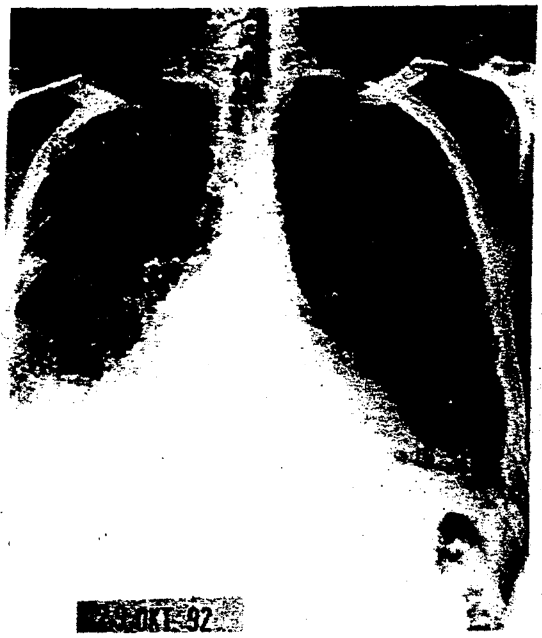

Fig. 1 The chest X-ray at the moment of referral to our outpatient clinic. It shows a fairly large amount of pleural fluid on the right side with some pleural thickening on the left side and a bilateral interstitial pattern.

< 15 UL^{-1}), ALAT 930 UL^{-1} (N < 15 UL^{-1}), LDH 1272 UL^{-1} (N < 160 UL^{-1}), alkaline phosphatase 99 UL^{-1} (N < 60 UL^{-1}), Gamma-GT 53 UL^{-1} (N < 28 UL^{-1}), serum IgE 165 IE ml^{-1} (N < 100 IE ml^{-1}), ACE normal. Autoantibodies (ANF) were not present. The urine analysis showed no abnormalities. Arterial blood sample: pH 7.44, pCO_2 3.5 kPa, pO_2 8.6 kPa, base excess −4 mmol L^{-1}, SaO_2 91%.

Lung function showed a restrictive pattern with a total lung capacity of 67% of the predicted amount. A mild obstruction was evident (FEV1/VC 70%) with a diminished carbonmonoxide diffusion (K_{CO} = 36% predicted).

The chest X-ray showed a fairly large amount of pleural fluid on the right side with some thickening of the pleura on the left side (Fig. 1). There was a reticular pattern located peripherally in the right lung and in the left lower lobe. There were no signs of left ventricular failure. The CT scan of the thorax confirmed the large amount of pleural fluid on the right side, and a reticular interstitial pattern in both lungs, more prominent on the right side, with thickened septa. Before any treatment was started, a fiberoptic bronchoscopy was performed. Cell counts in the bronchoalveolar fluid showed 12% epithelial cells, 34% eosinophils, 45% alveolar macrophages, 6% lymphocytes and only 3% neutrophils. Bacteriological examination including TBC culture and Ziehl-Neelsen stain of the lavage was negative, as were also the serological tests for Mycoplasma pneumoniae, Chlamydia and respiratory viruses. The cytological examination of the lavage showed reactive bronchial epithelial cells with eosinophilia. The transbronchial biopsies showed predominantly bronchial tissue and only a few alveoli, and were insufficient to diagnose an alveolar disease. The high number of eosinophils in the lavage led to the suspicion of a drug-induced interstitial lung disease [1]. Simvastin was considered the most probable cause, as it had been added to the patient's list of medication only recently. It was decided to discontinue this drug. A few days after the cessation of Simvastin, there was a significant improvement of his liverfunction tests (ASAT 100 UL^{-1}, ALAT 43 UL^{-1}, LDH 345 UL^{-1}). To further evaluate the effect of discontinuation of Simvastin, a bronchoscopy was repeated a few days later. This time the lavage fluid only showed a slight elevation of 16% neutrophils, 5% epithelial cells, 4% eosinophils, 70% macrophages and 5% lymphocytes. We decided to perform a right-sided thoracoscopy. There was darkish brown fluid in the pleural cavity. The parietal pleura showed no abnormalities. The visceral pleura appeared somewhat irregular with anthracosis most prominent in the upper lobes. Biopsies were taken from both the parietal and visceral pleura, and from the left lower lobe of the lung. Cultures showed no microorganisms. Light microscopy of the lung-biopsies showed diffuse fibrosis of the alveolar septa without specific hallmarks. Examination of the pleural fluid revealed non-specific findings. Two weeks after the cessation of Simvastin, the patient's clinical condition had not sufficiently improved and it was decided to prescribe prednisone 40 mg daily. His general condition then improved dramatically within a few days after starting the prednisone. An X-ray of the chest showed only a small amount of pleural fluid and a stationary interstitial pattern. The lung function test showed an improvement of the total lung capacity from 67 to 83% of the predicted amount. The obstructive component of his lung function remained unchanged as did the carbon monoxide diffusion. We decided to discharge the patient and to taper his prednisone dose. Shortly afterwards, he was admitted to another hospital in shock, highly suspected of having a gastric ulcer and Addison's crise. He died soon after admission. Post-mortem examination was not allowed.

Discussion

This patient with an extensive cardiac medical history was admitted to our hospital for analysis of recently developed interstitial lung disease and pleural effusion. Initially, the bronchoalveolar lavage contained an elevated level of eosinophils, which later returned to normal after discontinuation of Simvastin without any additional therapy. An infectious cause for his lung disease was excluded. Auto antibodies were not present and his ESR was only slightly elevated. There were no signs of arthritis or other systemic diseases. Therefore, autoimmune disease was very unlikely. The total IgE level in his serum was elevated. The patient was taking Simvastin for 6 months at admission, during which period he also developed his interstitial lung disease and pleural effusion. Though it does not prove a causal relation, the fact that the number of eosinophils in the bronchoalveolar lavage returned to normal without any additional therapy only a few days after the cessation of Simvastin makes the relationship very likely. Most of the known adverse effects of Simvastin are gastrointestinal. Hepatitis is the most serious complication which may be a reason to discontinue the drug.

A hypersensitivity syndrome has been reported (unpublished data from the manufacturer's product datasheet) with malaise, a lupus-like syndrome, hepatitis and dyspnea, but not with pulmonary or pleural involvement. Pulmonary and pleural disease resulting from the use of Simvastin has not been described before. Although the bronchoalveolar lavage fluid showed a remarkable decrease in the number of eosinophils, the general condition of our patient did not sufficiently improve. Therefore, we decided to prescribe orally administered corticosteroids (40 mg prednisone daily). After 2 days of using prednisone, the patient felt remarkably well and asked to be discharged from the hospital. His lung function test 3 weeks after the cessation of Simvastin and just 2 weeks after starting prednisone therapy showed a major improvement of the restrictive component. The total lung capacity improved from 67 to 83% of the predicted amount, his TLCO improved from 26 to 35% of the predicted amount.

To our knowledge, there are no reports of pulmonary or pleural adverse effects from the use of HMG-CoA reductase blockers. However, this patient shows that interstitial lung disease and pleural effusion may result from the use of Simvastin.

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Fatal lupus-like syndrome and ARDS induced by fluvastatin

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A woman aged 67 years was admitted to hospital with an 8-week history of polyarthralgia, aches and pains in the muscles, and a generalised rash. She was known to have hypertension, which was controlled with atenolol 50 mg daily. She had a history of retinal-vein thrombosis about 2 years before admission, after which she was placed on aspirin 75 mg daily. At a routine screening about 6 months before admission to hospital she was hypercholesteraemic, with a serum cholesterol of 7·2 mmol/L. Dietary measures were unsuccessful in lowering her cholesterol and she was placed on fluvastatin 20 mg daily. 1 week after she started the drug she noted an itchy, generalised, erythematous rash, followed by swelling and pain in her right knee and joints of both hands. She discontinued fluvastatin after about 10 weeks, but the symptoms had not resolved after more than 1 month after discontinuation of the drug, and she attended hospital

On admission she looked unwell. Her pulse rate was 92 beats per min; blood pressure 180/100 mm Hg. She was apyrexial. An erythematous maculopapular rash was seen mainly on sun-exposed areas. The facial rash was in a "butterfly" distribution. The small joints of the hands were swollen; there was periungal erythema and telangiectasia. Lung-field assessment showed crackles in both lung bases. Routine serum chemistry showed normal urea and electrolytes, raised concentration of C-reactive protein at 43 mg/L, mild derangement of liver function, and normal creatine kinase concentration. Full blood count was normal. Erythrocyte-sedimentation rate was 31 mm in the 1st h. Initial serum autoantibody screen was negative, as was rheumatoid factor; serum complement concentrations were normal; a subsequent test for double-stranded DNA by ELISA was positive at 274 (normal <50). Tests for antihistone and anticentromere antibodies were negative.

In the first few days after admission the patient became increasingly breathless. Lung-function tests showed a restrictive defect with decreased lung volumes (vital capacity 73% predicted with a normal forced expiratory volume in 1 s/forced vital capacity ratio) and diminished diffusing capacity (39% predicted). Analysis of serial arterial blood gases showed worsening type 1 respiratory failure. Computed tomography of the thorax showed extensive abnormalities of both lung fields, with possible widespread alveolitis and some areas of fibrosis. Bronchoscopy and bronchoalveolar lavage showed no endobronchial abnormality or opportunistic infection. Skin biopsy from an involved area showed a perivascular lymphocytic infiltrate in the dermis and areas of diffuse necrosis within the epidermis with incipient blister formation, features suggestive of subacute lupus, and erythema multiforme. An open lung biopsy revealed diffuse alveolar damage with hyaline membrane, intra-alveolar organisation, and atypical reactive pneumocytes characteristic of drug-induced lung damage, but no evidence of vasculitis or granuloma formation.

Shortly after admission, the patient's symptoms improved with non-steroidal anti-inflammatory drugs; however, the patient's respiratory status deteriorated progressively. High-dose steroids (pulsed intravenous methylprednisolone 1 g daily for 3 days) improved her skin lesions but her respiratory status continued to deteriorate. Despite assisted ventilation, and immunosuppressive therapy with cyclophosphamide, she died. At necropsy, the lungs showed signs of adult respiratory distress syndrome (ARDS). There was evidence of coronary atheroma; a small vegetation of uncertain relevance was noted on the mitral valve.

In general, statins (HMG Co-A reductase inhibitors) are well tolerated and have been shown to be effective in the primary and secondary prevention of coronary heart disease.[1,2] There have been previous reports of lupus-like syndrome in patients on statins.[3,4] In the cases involving lovastatin[3] and simvastatin,[4] the symptoms were mild and resolved when the statin was stopped and small doses of oral steroids started. One patient with systemic lupus erythematosus induced by lovastatin had features of pulmonary involvement with radiological appearances of pneumonitis.[3]

We could not identify previous reports of fatal lupus-like reaction with pulmonary toxicity resulting in an ARDS-like syndrome. No such effects have been reported to the Committee on Safety of Medicine in the UK or manufacturers of statins (personal communications). Our findings may show a class effect rather than an effect restricted to an individual statin. Since the illness was severe and rapidly led to death, it was not possible to fulfil conventional criteria for diagnosis of a drug-induced reaction. The absence of other causes for the clinical syndrome described, previous reports of a similar (albeit milder) cases, the temporal relation of the symptoms to the drug therapy, and the characteristic toxic appearances on lung biopsy argue in favour of an adverse reaction to fluvastatin. A single fatality from a side-effect should not alter prescribing policy, but should lead to greater vigilance and awareness of the potential side-effects and early withdrawal of treatment should suggestive systems occur.

We thank J Parmar for doing the open lung biopsy; S Rogerson for his report on the lung biopsy; Gill Douce, Stephanie Munn, and S Humphreys for their reports on the skin biopsy; and Valerie Suarez for her necropsy report.

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Nutrient intakes among UK African-Caribbeans: changing risk of coronary heart disease

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Coronary heart disease (CHD) mortality in the UK for Caribbean-born people, who are mainly of African descent, continues at less than half the national average for men, and two-thirds for women.[1] Nutrient intake is a major contributor to coronary risk but little dietary information is available for the African-Caribbean population in Britain.

We developed a specific food-frequency questionnaire (FFQ) with the local African-Caribbean community to assess food consumption during the previous 12 months. This was part of an international study;[2] in the UK, a random sample of people aged 25–79 years from four general-practice population registers serving inner-city

Simvastatin-Induced Lupus Erythematosus

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ABSTRACT: We report the case of a 79-year-old man who had onset of fatigue, myalgia, and pleuritic chest pain 3 months after initiation of therapy with simvastatin. He had signs of pleuropericarditis due to simvastatin-induced lupus erythematosus. This should alert clinicians to this possible adverse effect of simvastatin and other statins.

DRUG-INDUCED LUPUS is a fairly common problem, and more and more therapeutic agents have been found to cause it. We report a case of simvastatin-induced lupus erythematosus.

CASE REPORT

A 79-year-old white man with primary hypercholesterolemia was started on simvastatin (Zocor) in March 1996. In June 1996, he was admitted to the hospital with fatigue, myalgia, shortness of breath, and right-sided pleuritic chest pain. Physical examination revealed low-grade temperature and signs of right-sided pleural effusion. The chest x-ray film confirmed this, along with the possibility of infiltrate vs atelectases in the right lung base. Electrocardiogram (ECG), cardiac enzymes, and ventilation perfusion lung scan were unremarkable. Thoracentesis revealed exudative fluid with prominent eosinophilia (28%). A peripheral smear, however, did not show any eosinophilia. Gram's stain, acid-fast bacilli smear, postassium hydroxide smear, cultures, and cytology of the pleural fluid were unremarkable. The patient was started on erythromycin and cefuroxime therapy.

The patient did not improve, and pleural fluid rapidly reaccumulated. The ECG showed widespread ST segment elevation, suggestive of pericarditis: A 2-D echocardiogram showed mild pericardial effusion with preserved left ventricular function. Pulmonary artery catheterization revealed normal right atrial, ventricular, pulmonary artery, and wedge pressures, ruling out heart failure as a possible cause of the pleural effusion. Computed tomography of the chest showed bilateral pleural effusion, with minimal atelectases at the right lung base. No mass lesion was seen. Findings on viral, fungal, and lyme serology studies were normal.

Further workup revealed an elevated erythrocyte sedimentation rate (109/hr), strongly positive antinuclear antibody titer (1:320), and strongly positive antihistone antibody titer of 1.5 (normal, <1). Anti-DNA, anti-Ro antibody, anti-La antibody, and rheumatoid factor were negative. Repeated thoracentesis showed exudative fluid and eosinophilia (23%) and was positive for antinuclear antibody. These findings pointed toward simvastatin-induced lupus erythematosus, and the drug was withdrawn. The patient was started on prednisone (40 mg daily) with good response. The fever, shortness of breath, pleuritic chest pain, and pleural effusion rapidly improved, and he was discharged home.

On follow-up, the chest x-ray film showed no effusion. The ESR, antihistone antibody titer, and antinuclear antibody titer came back to normal within 2 weeks. Prednisone was tapered off over a period of 2 weeks. The patient has been asymptomatic since that time.

DISCUSSION

Approximately 30,000 to 50,000 individuals in the United States have drug-induced lupus. This represents 5% to 10% of the total number of patients who have systemic lupus erythematosus.[1,2] There is no consensus on the diagnostic criteria for drug-induced lupus. It should be suspected in patients who do not have a history of idiopathic lupus, who have antinuclear antibody and at least one clinical feature of lupus after an appropriate duration of drug treatment, and whose symptoms resolve after discontinuing the drug.[3] Our case aptly illustrates this hypothesis.

More than 70 drugs have been reported to cause a lupus-like illness or exacerbate preexisting lupus,[3] with procainamide[1,4] being the most common offender. A few cases have been reported with lovastatin,[5,6,7] a first-generation 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. To date, only one case of simvastatin-induced lupus[8] has been reported. Our case supports this finding and brings attention to the possible adverse effects of the newer biosynthetic statins. As the number of patients being treated with statins increases, clinicians should expect to see more of such cases and be alert to this complication of therapy.

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Lupus-like syndrome associated with simvastatin

Sir—M K Sridhar and A Abdulla's (July 11, p 114)[1] report is unfortunately not the only such experience of a lupus-like syndrome associated with the use of the statin group of drugs.

In 1996, a 39-year-old self-employed food worker presented with a 6-week history of numbness, predominantly in his right hand when extracting food from the deep freeze. He also reported pallor and numbness on exercise to the extent that he would have difficulty in releasing the grip on his tennis racquet. Further inquiry revealed occasional joint pain, but no swelling affecting the carpometacarpel joint of the thumb and wrist bilaterally. He gave a history of a malignant melanoma excised from the skin overlying the left shoulder in 1991 with subsequent axillary clearance in 1995. The malignant lesion was felt to be in remission at the time of these events. In 1974, he had had splenectomy after a road accident He had been taking simvastatin 20 mg daily for 4 years.

Examination showed typical colour changes of Raynaud's phenomenon with a positive Allen's test for poor collateral circulation between the ulnar and radial arteries. There were no other signs to suggest vasculitis; no rash, no cardiorespiratory signs, and no myotonia. Investigation revealed a positive antinuclear antibody (ANA) titre greater than 2560 with a speckled pattern, there were no antibodies to DNA or extractable nuclear antigen or histone, and he had normal complement and immunoglobulin values, negative cryoglobulin studies, and a negative Coomb's test. Simvastatin was stopped and nifedipine started to reduce his Raynaud's symptoms. He was given advice on cold exposure. After 2 months all symptoms were improving, at 5 months mild Raynaud's persisted with slight restriction of flexion in his fingers. At 1 year his ANA titre remained greater than 2560.

Although a much more mild case than that described by Sridhar and Abdulla, this observation does suggest that similar problems, of varying severity, may be affecting patients taking this class of drug and we support these workers' recommendation for vigilance.

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Oxyphilic parathyroid adenoma and lithium therapy

Sir—A cause of hypercalcaemia, not reported by David A Bushinsky and co-workers (July 25, p 306),[1] is hyperparathyroidism induced by lithium therapy. Lithium carbonate is widely used to treat manic-depressive psychosis. After several years of lithium therapy, 10% of patients have raised serum total calcium and intact parathyroid hormone (iPTH),[2] and 40% have serum ionised calcium above the reference range.[3] In-vitro studies provide strong evidence that lithium can induce direct stimulation of PTH secretion,[4] and increase parathyroid cell mass.[5] Hypercalcaemia is usually a reversible condition, remitting when lithium is stopped. In a few individuals, long-term stimulation of parathyroid cells may lead to the development of parathyroid tumours. We report a case of lithium-induced hyperparathyroidism.

A 51-year-old white man with a 20 year history of bipolar psychiatric disorder was admitted in May, 1996, because of nausea and vomiting for 7 days and anorexia with 8 kg weight reduction over 3 months. He had been treated with lithium carbonate (750 mg daily) for more than 10 years. A cholecystectomy had been undertaken for cholelithiasis, and he had had several episodes of renal colic, with urinary stone explusion in 1989. In May, 1992, his calcium serum concentration was 2·5 mmol/L and in April, 1995, it was 2·9 mmol/L. On physical examination he was alert and oriented. Neck palpation was normal. Laboratory data showed: serum calcium 3·08 mmol/L, phosphate 0·77 mmol/L, creatinine 90 [illegible]L, albumin 46 g/L, magnesium [illegible]82 mmol/L, thyrotropin 0·99 m[illegible]mL (normal 0·3–5·0), [illegible] concentration 0·4 mmol/L (0·1[illegible]6), and iPTH 110 ng/L (0–65); 24-h urinary calcium excretion 31 mmol (2·5–7·5), phosphate excretion 40 mmol (12·9–42), and hydroxyproline excretion 55 mg (15–45).

He was treated with 5 I isotonic saline and furosemide 40 mg for 24 h. Later, as calcium serum decreased to 2·7 mmol/L, intravenous perfusion was stopped and a minimum of 3 L water ingestion daily was recommended. In February, 1997, because hyperparathyroidism persisted although lithium therapy had been discontinued, a bilateral neck exploration was done. At surgery, parathyroid glands seemed enlarged. Two nodular areas were discovered, one in the right upper parathyroid gland and one in the right thyroid lobule which measured 30×15×10 mm and 20×10×15 mm, respectively. Both nodules, and two other parathyroid glands were excised. Histological examination of thyroid showed a follicular adenoma. In the parathyroid gland, we identified a well defined nodule weighing 1·2 g, which is consistent with an oxyphilic adenoma. Microscopically, the other two parathyroid glands had a normal distribution of all cell types, and normal areas of fat. Since surgery, iPTH and serum calcium have remained normal.

The pathology in litium-induced hyperparathyroidism is adenoma in a single gland or hyperplasia or all glands, as seen in primary disease. Oxyphillic are more rare and tend to be larger than chief cells adenomas, and serum calcium tends to be minimally increased. Under chronic stimulation by lithium, adenoma development may be regarded as the analogous of tertiary hyperparathyroidism in chronic renal failure or vitamin D deficiency.

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PHYSICIAN'S DESK REFERENCE (PDR) 1999

...inhibit the activity of this isozyme ...metabolizers resemble poor metabolizers. ...table on a given dose of TCA may be- ...when given one of these inhibiting ...therapy. The drugs that inhibit cyto- ...include some that are not metabolized by ...cimetidine) and many that are sub- ...(many other antidepressants, pheno- ...Type 1C antiarrhythmics, propafenone ...all the selective serotonin reuptake ...fluoxetine, sertraline, and paroxet- ...they may vary in the extent of inhi- ...which SSRI-TCA interactions may pose ...depend on the degree of inhibition and ...of the SSRI involved. Nevertheless, ...in the coadministration of TCAs with ...also in switching from one class to the ...importance, sufficient time must elapse ...TCA treatment in a patient being with- ...given the long half-life of the parent ...(at least 5 weeks may be necessary). ...tricyclic antidepressants with drugs ...cytochrome P450 2D6 may require lower ...prescribed for either the tricyclic antide- ...other drug. Furthermore, whenever one of ...is withdrawn from co-therapy, an in- ...tricyclic antidepressant may be required. It ...TCA plasma levels whenever a TCA ...administered with another drug known to ...P450 2D6.

...effectiveness of VIVACTIL in pediatric pa- ...been established.

...ACTIONS

...the following adverse reactions are ...decreasing severity. Included in the listing ...reactions which have not been reported ...drug. However, the pharmacological simi- ...tricyclic antidepressant drugs require ...reactions be considered when protriptyline ...VIVACTIL is more likely to aggravate agi- ...and produce cardiovascular reactions ...and hypotension.

...Myocardial infarction; stroke; heart ...hypotension, particularly orthostatic ...tachycardia; palpitation.

...states (especially in the elderly) ...disorientation, delusions, anxiety, rest- ...hypomania; exacerbation of psychosis; ...nightmares.

...seizures; incoordination; ataxia; tremors; ...numbness, tingling, and paresthe- ...extrapyramidal symptoms; drowsiness; ...and fatigue; headache; syndrome of in- ...antidiuretic hormone) secretion; tinnitus; ...patterns.

...paralytic ileus; hyperpyrexia; urinary re- ...micturition, dilatation of the urinary tract; ...vision, disturbance of accommodation, ...pressure, mydriasis; dry mouth and ...sublingual adenitis.

...petechiae, skin rash, urticaria, itch- ...(avoid excessive exposure to sun- ...or of face and tongue).

...agranulocytosis; bone marrow depression; ...thrombocytopenia; purpura; eosinophilia.

...Nausea and vomiting; anorexia; epigas- ...peculiar taste; stomatitis; abdominal

...increased or decreased libido; gyn- ...male; breast enlargement and galactor- ...testicular swelling; elevation or depres- ...sugar levels.

...(simulating obstructive); altered liver ...swelling; alopecia; flushing; weight gain or ...frequency, nocturia; perspiration.

...Symptoms: Though not indicative of addic- ...of treatment after prolonged therapy ...nausea, headache, and malaise.

...AND ADMINISTRATION

...be initiated at a low level and increased ...carefully the clinical response and any ev-

...Dosage—Fifteen to 40 mg a day divided into ...If necessary, dosage may be increased to 60 ...dosages above this amount are not recom- ...should be made in the morning dose. ...*Elderly Patients*—In general, lower dos- ...recommended for these patients. Five mg 3 ...be given initially, and increased gradu- ...In elderly patients the cardiovascular

When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.

Minor adverse reactions require reduction in dosage. Major adverse reactions or evidence of hypersensitivity require prompt discontinuation of the drug.

The safety and effectiveness of VIVACTIL in pediatric patients have not been established.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

MANIFESTATIONS

Critical manifestations of overdosage include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

MANAGEMENT

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose. These patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of a tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a pCO_2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide). In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

NDC 0006-0026-68 bottles of 100
(6505-00-369-7297, 5 mg 100).
Shown in Product Identification Guide, page 323

No. 3314—Tablets VIVACTIL, 10 mg, are yellow, oval, film coated tablets, coded MSD 47. They are supplied as follows:
NDC 0006-0047-68 bottles of 100
(6505-00-462-7353, 10 mg 100's)
NDC 0006-0047-28 unit dose packages of 100.
Shown in Product Identification Guide, page 323

Storage

Store Tablets VIVACTIL in a tightly closed container. Avoid storage at temperatures above 40°C (104°F).

METABOLISM

Metabolic studies indicate that protriptyline is well absorbed from the gastrointestinal tract and is rapidly sequestered in tissues. Relatively low plasma levels are found after administration, and only a small amount of unchanged drug is excreted in the urine of dogs and rabbits. Preliminary studies indicate that demethylation of the secondary amine moiety occurs to a significant extent, and that metabolic transformation probably takes place in the liver. It penetrates the brain rapidly in mice and rats, and moreover that which is present in the brain is almost all unchanged drug.

Studies on the disposition of radioactive protriptyline in human test subjects showed significant plasma levels within 2 hours, peaking at 8 to 12 hours, then declining gradually. Urinary excretion studies in the same subjects showed significant amounts of radioactivity in 2 hours. The rate of excretion was slow. Cumulative urinary excretion during 16 days accounted for approximately 50% of the drug. The fecal route of excretion did not seem to be important.

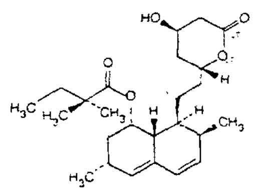
7904023 Issued July 1996

ZOCOR® Tablets ℞
(Simvastatin)

DESCRIPTION

ZOCOR* (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as preservative.

*Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein (LDL) cholesterol in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL (low-density lipoprotein) cholesterol and low HDL

Continued on next page

Zocor—Cont.

[illegible]igh-density lipoprotein) cholesterol are both risk factors [illegible]r coronary heart disease. Though frequently found in as[illegible]ociation with low HDL, elevated plasma triglycerides (TG) [illegible]as not been established as an independent risk factor for [illegible]ronary heart disease. The independent effect of raising [illegible] or lowering TG on the risk of coronary and cardiovas[illegible]lity and mortality has not been determined. [illegible] [illegible]dinavian Simvastatin Survival Study (4S), the [illegible]ffect of improving lipoprotein levels with ZOCOR on total [illegible]ortality was assessed in 4444 patients with coronary [illegible]eart disease (CHD) and baseline total cholesterol (TO[illegible]AL-C) 212–309 mg/dL (5.5–8.0 mmol/L). The patients were [illegible]llowed for a median of 5.4 years. In this multicenter, ran[illegible]omized, double-blind, placebo-controlled study, ZOCOR [illegible]gnificantly reduced the risk of mortality by 30% (11.5% vs [illegible]2%, placebo vs ZOCOR); of CHD mortality by 42% (8.5% [illegible] 5.0%); and of having a hospital-verified non-fatal myocar[illegible]ial infarction by 37% (19.6% vs 12.9%). Furthermore, ZO[illegible]OR significantly reduced the risk for undergoing myocar[illegible]ial revascularization procedures (coronary artery bypass [illegible]rafting or percutaneous transluminal coronary angio[illegible]lasty) by 37% (17.2% vs 11.4%) [see CLINICAL PHARMA[illegible]OLOGY, *Clinical Studies*].

[illegible]OCOR has been shown to reduce both normal and elevated [illegible]DL cholesterol concentrations. LDL is formed from very-[illegible]ow-density lipoprotein (VLDL) and is catabolized predomi[illegible]antly by the high affinity LDL receptor. The mechanism of [illegible]he LDL-lowering effect of ZOCOR may involve both reduc[illegible]ion of VLDL cholesterol concentration, and induction of the [illegible]DL receptor, leading to reduced production and/or in[illegible]reased catabolism of LDL cholesterol. Apolipoprotein B [illegible]Apo B) also falls substantially during treatment with ZO[illegible]OR. As each LDL particle contains one molecule of apoli[illegible]oprotein B, and since in patients with predominant eleva[illegible]ions in LDL-C (without accompanying elevation in VLDL) [illegible]ittle apolipoprotein B is found in other lipoproteins, this [illegible]trongly suggests that ZOCOR does not merely cause cho[illegible]esterol to be lost from LDL, but also reduces the concentra[illegible]ion of circulating LDL particles. In addition, ZOCOR re[illegible]uces VLDL cholesterol and plasma triglycerides (TG) and [illegible]ncreases HDL cholesterol. The effects of ZOCOR on Lp(a), [illegible]ibrinogen, and certain other independent biochemical risk [illegible]arkers for coronary heart disease are unknown.

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an e[illegible]o in the biosynthetic pathway for cholesterol.

P[illegible]kinetics

Sim[illegible]tin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an A.H.A. recommended low-fat meal.

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

Clinical Studies

ZOCOR has been shown to be highly effective in reducing total and LDL cholesterol in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4–6 weeks. The response was maintained during chronic therapy. Furthermore, improving lipoprotein levels with ZOCOR improved survival in patients with CHD and hypercholesterolemia treated with 20–40 mg per day for a median of 5.4 years.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial or non-familial hypercholesterolemia, ZOCOR given as a single-dose in the evening (the recommended dosing) was similarly effective as when given on a twice-daily basis. ZOCOR consistently and significantly decreased total plasma cholesterol (TOTAL-C), LDL cholesterol (LDL-C), total cholesterol/HDL cholesterol (TOTAL-C/HDL-C) ratio, and LDL cholesterol/HDL cholesterol (LDL-C/HDL-C) ratio. ZOCOR also decreased triglycerides (TG) and increased HDL cholesterol (HDL-C).

The results of 3 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia are presented in TABLE I.

[See table I below]

The mean reduction in LDL cholesterol was 47% at the 80-mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma triglycerides ≤ 200 mg/dL had a median reduction in triglycerides of 21%, while in 189 patients with triglycerides > 200 mg/dL, the median reduction in triglycerides was 36%. In these studies, patients with triglycerides > 350 mg/dL were excluded.

In a controlled clinical study, 12 patients 15–39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of the 12 patients had reductions in LDL cholesterol. In those pati[illegible] reductions, the mean LDL cholesterol change[illegible] and 80-mg doses were 14% (range 8% to 23%, [illegible] and 30% (range 14% to 46%, median 29%), respectiv[illegible] patient had an increase of 15% in LDL cholesterol[illegible] patient with absent LDL cholesterol receptor [illegible] an LDL cholesterol reduction of 41% with the 80-[illegible]

In the Scandinavian Simvastatin Survival Study [illegible] effect of therapy with ZOCOR on total mortality [illegible] sessed in 4444 patients with coronary heart d[illegible] and baseline total cholesterol 212–309 mg/dL [illegible] mmol/L). In this multicenter, randomized, double-[illegible] cebo-controlled study, patients were treated with [illegible] care, including diet, and either ZOCOR 20–40 mg [illegible] (n=2221) or placebo (n=2223) for a median durat[illegible] years. Over the course of the study, treatment with [illegible] led to mean reductions in total cholesterol, LDL [illegible] and triglycerides of 25%, 35%, and 10%, respectiv[illegible] mean increase in HDL cholesterol of 8%. ZOCOR [illegible] cantly reduced the risk of mortality (Figure 1) [illegible] (p=0.0003, 182 deaths in the ZOCOR group vs 256 [illegible] the placebo group). The risk of CHD mortality [illegible] cantly reduced by 42%, (p=0.00001, 111 vs 189). [illegible] no statistically significant difference between [illegible] cardiovascular mortality. ZOCOR also signif[illegible] creased the risk of having major coronary events [illegible] tality plus hospital-verified and silent non-fatal [illegible] infarction [MI]) (Figure 2) by 34%, (p<0.00001, [illegible] vs 622 patients with one or more events). The ris[illegible] a hospital-verified non-fatal MI was reduced [illegible] ZOCOR significantly reduced the risk for under[illegible] cardial revascularization procedures (coronary [illegible] pass grafting or percutaneous transluminal coro[illegible] oplasty) by 37%, (p<0.00001, 252 patients vs 383 [illegible] Furthermore, ZOCOR significantly reduced the [illegible] plus non-fatal cerebrovascular events (combined [illegible] transient ischemic attacks) by 28% (p=0.033, 75 [illegible] 102 patients). ZOCOR reduced the risk of major [illegible] events to a similar extent across the range of [illegible] and LDL cholesterol levels. The risk of mortality [illegible] icantly decreased in patients ≥60 years of age [illegible] in patients <60 years of age by 37%. Because [illegible] only 53 female deaths, the effect of ZOCOR on [illegible] women could not be adequately assessed. How[illegible] significantly lessened the risk of having major [illegible] events by 34% (60 women vs 91 women with [illegible] event). The randomization was stratified by [illegible] (21% of each treatment group) or a previous [illegible] there were only 57 deaths among the patients [illegible] alone at baseline, the effect of ZOCOR on [illegible] subgroup could not be adequately assessed[illegible] trends in reduced coronary mortality, major co[illegible] and revascularization procedures were consis[illegible] *this group and the total study cohort.*

Figure 1

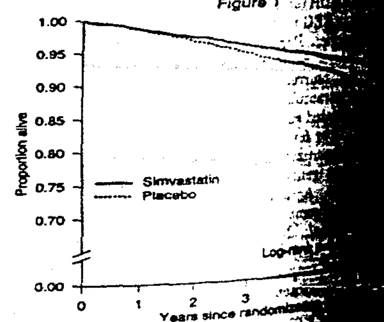
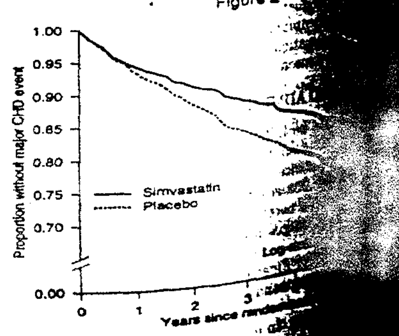


Figure 2



In the Multicenter Anti-Atheroma Stu[illegible] apy with simvastatin on atheroscler[illegible]

Table I
Dose Response in Patients with Primary Hypercholesterolemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study (Mean % Change at Week 6)					
ZOCOR					
5 mg q.p.m.	109	−19	−26	10	−12
10 mg q.p.m.	110	−23	−30	12	−15
Scandinavian Simvastatin Survival Study (Mean % Change at Week 6)					
Placebo	2223	−1	−1	0	3
ZOCOR					
20 mg q.p.m.	2221	−28	−38	8	−15
Upper Dose Comparative Study (Mean % Change averaged at Weeks 18 and 24)					
Z[illegible]					
[illegible] p.m.	433	−31	−41	9	−18
8[illegible]g q.p.m.	664	−36	−47	8	−24

* median percent change

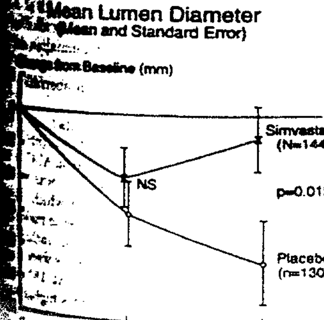
) In th[illegible]
erol [illegible]
% (range 8% to [illegible]
5%, median 29%[illegible]
of 15% in LDL[illegible]
. cholesterol re[illegible]
ction of 41% with[illegible]
vastatin Surviva[illegible]
OCOR on total[illegible]
with coronary he[illegible]
lesterol 212–309[illegible]
ter, randomized[illegible]
tients were trea[illegible]
d either ZOCOR[illegible]
223) for a media[illegible]
the study, treat[illegible]
n total cholester[illegible]
. 35%, and 10%[illegible]
cholesterol of 8[illegible]
of mortality (R[illegible]
the ZOCOR grou[illegible]
risk of CHD m[illegible]
p=0.00001, [illegible]
it difference betw[illegible]
y. ZOCOR also[illegible]
g major coronary[illegible]
ied and silent no[illegible]
2) by 34%, (p<0.0[illegible]
or more events[illegible]
n-fatal MI was[illegible]
duced the risk fo[illegible]
n procedures (co[illegible]
aneous translum[illegible]
0001, 252 patient[illegible]
gnificantly redu[illegible]
scular events (co[illegible]
ks) by 28% (p=0.0[illegible]
reduced the risk[illegible]
nt across the ra[illegible]
els. The risk of [illegible]
60 years[illegible]
37%[illegible]
h of ZOCO[illegible]
quately assessed[illegible]
the risk of havi[illegible]
nen vs 91 wome[illegible]
tion was strati[illegible]
group) or a [illegible]
ths among the [illegible]
fect of ZOCOR [illegible]
e adequately [illegible]
ary mortality, m[illegible]
rocedures were [illegible]
study cohort.[illegible]

Two or More Other Risk Factors††	LDL-Cholesterol mg/dL (mmol/L) Initiation Level	Goal
NO	≥190 (≥4.9)	<160 (<4.1)
YES	≥160 (≥4.1)	<130 (<3.4)
YES OR NO	≥130††† (≥3.4)	≤100 (≤2.6)

[illegible]heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
[illegible] factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature [illegible] without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hy[illegible] confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is [illegible] (≥1.6 mmol/L).
[illegible] patients with LDL-C levels 100–129 mg/dL, the physician should exercise clinical judgment in deciding [illegible] initiate drug treatment.

[illegible] coronary angiography in hypercholesterolemic [illegible] with coronary heart disease. In this ran[illegible] blind, controlled trial, patients with a [illegible] total cholesterol value of 245 mg/dL (6.4 [illegible] mean baseline LDL value of 170 mg/dL (4.4 [illegible] treated with conventional measures and with [illegible] mg/day or placebo. Angiograms were evalu[illegible] two and four years. A total of 347 patients [illegible] angiogram and at least one follow-up angio[illegible] primary endpoints of the trial were mean [illegible] in minimum and mean lumen diam[illegible] focal and diffuse disease, respectively. Sim[illegible] significantly slowed the progression of lesions as [illegible] the final angiogram by both these parameters [illegible] in minimum lumen diameter: −0.04 mm [illegible] vs −0.12 mm with placebo; mean changes [illegible] diameter: −0.03 mm with simvastatin vs [illegible] placebo), as well as by change from baseline [illegible] stenosis (0.9% simvastatin vs 3.6% pla[illegible] years, the groups also differed significantly [illegible] of patients categorized with disease pro[illegible] simvastatin vs 33% placebo) and disease re[illegible] simvastatin vs 12% placebo). In addition, [illegible] significantly decreased the proportion of pa[illegible] lesions (13% simvastatin vs 24% placebo) [illegible] total occlusions (5% vs 11%). The mean [illegible] in mean and minimum lumen diameters [illegible] comparing angiograms in the subset of 274 [illegible] had matched angiographic projections at base[illegible] four years is presented below (Figures 3 and [illegible]

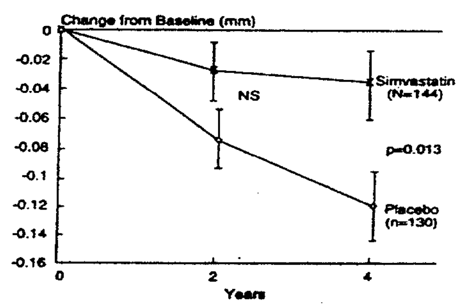
Figure 3



[illegible] at top of next column]

[illegible] studies, simvastatin did not impair adrenal re[illegible] significantly reduce basal plasma cortisol concen[illegible] reductions from baseline in basal plasma tes[illegible] were observed in clinical studies with sim[illegible] effect also observed with other inhibitors of [illegible] reductase and the bile acid sequestrant [illegible] there was no effect on plasma gonadotro[illegible] placebo-controlled 12-week study there was [illegible] effect of simvastatin 80 mg on the plasma tes[illegible] to hCG. In another 24-week study simv[illegible] had no detectable effect on spermatogen[illegible]

Figure 4



cause of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence of coronary heart disease, or other risk factors. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate (see NCEP Guidelines, below).

Coronary Heart Disease

In patients with coronary heart disease and hypercholesterolemia, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures.
- Reduce the risk of stroke or transient ischemic attack.

(For a discussion of efficacy results by gender and other predefined subgroups, see CLINICAL PHARMACOLOGY, *Clinical Studies.*)

Hyperlipidemia

ZOCOR is indicated as an adjunct to diet to reduce elevated TOTAL-C LDL-C, Apo B, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb**).

ZOCOR is also indicated to reduce TOTAL-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

General Recommendations

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure TOTAL-C, HDL-C, and triglycerides. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

mined by ultracentrifugation. In many hypertriglycer[illegible] patients, LDL-C may be low or normal despite elevat[illegible] TAL-C. In such cases, ZOCOR is not indicated.

Lipid determinations should be performed at interva[illegible] less than four weeks and dosage adjusted according [illegible] patient's response to therapy.

The National Cholesterol Education Program ([illegible] Treatment Guidelines are summarized below:

[See table at left]

At the time of hospitalization for an acute coronary [illegible] consideration can be given to initiating drug therapy [illegible] charge if the LDL-C is ≥ 130 mg/dL (see NCEP Guid[illegible] above).

Since the goal of treatment is to lower LDL-C, the [illegible] recommends that LDL-C levels be used to initiate a[illegible] sess treatment response. Only if LDL-C levels are not [illegible] able, should the TOTAL-C be used to monitor therap[illegible]

ZOCOR is indicated to reduce elevated LDL cholester[illegible] triglyceride levels in patients with Type IIb hyperlipo[illegible] inemia (where hypercholesterolemia is the major abn[illegible] ity). However, it has not been studied in conditions [illegible] the major abnormality is elevation of chylomicrons, [illegible] or IDL (i.e., hyperlipoproteinemia types I, III, IV, or [illegible]

**Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations major	min[illegible]
I (rare)	chylomicrons	TG	↑—
IIa	LDL	C	—
IIb	LDL, VLDL	C	T[illegible]
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑—
V (rare)	chylomicrons, VLDL	TG	↑—

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very-low-density lipoprotein,
IDL = intermediate-density lipoprotein.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication[illegible]

Active liver disease or unexplained persistent elevati[illegible] serum transaminases (see WARNINGS).

Concomitant therapy with the tetralol-class calcium [illegible] nel blocker mibefradil (see PRECAUTIONS, *Drug In[illegible] tions*).

Pregnancy and lactation. Atherosclerosis is a chron[illegible] cess and the discontinuation of lipid-lowering drugs [illegible] pregnancy should have little impact on the outcome o[illegible] term therapy of primary hypercholesterolemia. Mor[illegible] cholesterol and other products of the cholesterol bios[illegible] sis pathway are essential components for fetal develop[illegible] including synthesis of steroids and cell membrane[illegible] cause of the ability of inhibitors of HMG-CoA red[illegible] such as ZOCOR to decrease the synthesis of cholester[illegible] possibly other products of the cholesterol biosynthesis [illegible] way, ZOCOR is contraindicated during pregnancy a[illegible] nursing mothers. **ZOCOR should be administere[illegible] women of childbearing age only when such patien[illegible] highly unlikely to conceive.** If the patient becomes pre[illegible] while taking this drug, ZOCOR should be discontinu[illegible] mediately and the patient should be apprised of the [illegible] tial hazard to the fetus (see PRECAUTIONS, *Pregna[illegible]*

WARNINGS

Skeletal Muscle

Simvastatin and other inhibitors of HMG-CoA reducta[illegible] casionally cause myopathy, which is manifested as [illegible] pain or weakness associated with grossly elevated cre[illegible] kinase (> 10X the upper limit of normal [ULN]). **Rhabd[illegible] olysis, with or without acute renal failure seconda[illegible] myoglobinuria, has been reported rarely.** In the Scan[illegible] vian Simvastatin Survival Study, there was one case [illegible] opathy among 1399 patients taking simvastatin 20 m[illegible] no cases among 822 patients taking 40 mg daily for [illegible] dian duration of 5.4 years. In two 6-month controlled [illegible] cal studies, there was one case of myopathy among 4[illegible] tients taking 40 mg and 5 cases among 669 patients t[illegible] 80 mg. The risk of myopathy is increased by concon[illegible] therapy with certain drugs, some of which were exclud[illegible] the designs of these studies (see below).

Myopathy caused by drug interactions.

The incidence and severity of myopathy are increas[illegible] concomitant administration of HMG-CoA reductase i[illegible]

Continued on next p[illegible]

tors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic [illegible]way can raise the plasma levels of simvastatin and may [illegible]se the risk of myopathy. These include cyclosporine, [illegible]conazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, and the antidepressant nefazodone.

Reducing the risk of myopathy.

1. General measures. Patients starting therapy with simvastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. **Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with simvastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to simvastatin typically provides lit[illegible]e additional reduction in LDL cholesterol, but further re[illegible]uctions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg (see DOSAGE AND ADMINISTRATION, *General Recommendations and Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Interruption of simvastatin therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the Scandinavian Simvastatin Survival Study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the number of patients with more than one transaminase elevation to >3 times the upper limit of normal, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3 times the upper limit of normal and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of [illegible]statin; 37% were titrated to 40 mg.

In 2 [illegible]led clinical studies in 1105 patients, the 12-[illegible]ce of persistent hepatic transaminase eleva[illegible]ard to drug relationship was 0.9% and 2.1% [illegible]-mg dose, respectively. No patients devel[illegible]er function abnormalities following the [illegible]reatment at a given dose.

It is recommended that liver function tests be performed **before the initiation of treatment, and periodically thereafter (e.g., semiannually) for the first year of treatment or until one year after the last elevation in dose. Patients titrated to the 80 mg dose should receive an additional test at 3 months.** Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

PRECAUTIONS

General

Simvastatin may cause elevation of creatine kinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness (see WARNINGS, *Skeletal Muscle*).

Drug Interactions

Mibefradil (see CONTRAINDICATIONS), *Cyclosporine, Itraconazole, Ketoconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin, Clarithromycin, Nefazodone:* See WARNINGS, *Skeletal Muscle*.

Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolized by the cytochrome P-450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform (see WARNINGS, *Skeletal Muscle*).

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20–40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs in a mean plasma drug level similar to that seen with the [illegible] mg/kg/day dose.

CNS vascular lesions, characterized by perivascular [illegible]rhage and edema, mononuclear cell infiltration of per[illegible]cular spaces, perivascular fibrin deposits and necro[illegible] small vessels were seen in dogs treated with simvastatin [illegible] a dose of 360 mg/kg/day, a dose that produced mean [illegible] drug levels that were about 14 times higher than the [illegible] drug levels in humans taking 80 mg/day. Similar CNS [illegible]cular lesions have been observed with several other drugs [illegible] this class.

There were cataracts in female rats after two years of [illegible]ment with 50 and 100 mg/kg/day (22 and 25 times the [illegible]man AUC at 80 mg/day, respectively) and in dogs after [illegible] months at 90 mg/kg/day (19 times) and at two years [illegible] mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were admi[illegible] daily doses of simvastatin of 25, 100, and 400 mg/kg [illegible] weight, which resulted in mean plasma drug levels [illegible]imately 1, 4, and 8 times higher than the mean [illegible] plasma drug level, respectively (as total inhibitory [illegible] based on AUC) after an 80-mg oral dose. Liver car[illegible] were significantly increased in high-dose females and [illegible] and high-dose males with a maximum incidence of [illegible]cent in males. The incidence of adenomas of the liv[illegible] significantly increased in mid- and high-dose females [illegible] treatment also significantly increased the incidence of [illegible] adenomas in mid- and high-dose males and females [illegible]enomas of the Harderian gland (a gland of the eye [illegible]dents) were significantly higher in high-dose mice [illegible] controls. No evidence of a tumorigenic effect was [illegible] at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice [illegible] up to 25 mg/kg/day, no evidence of a tumorigenic [illegible] observed (mean plasma drug levels were 1 times [illegible] than humans given 80 mg simvastatin as measured [illegible] AUC).

In a two-year study in rats at 25 mg/kg/day, there [illegible] statistically significant increase in the incidence of [illegible] follicular adenomas in female rats exposed to appr[illegible] 11 times higher levels of simvastatin than in humans [illegible] 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with [illegible] and 100 mg/kg/day produced hepatocellular ade[illegible] carcinomas (in female rats at both doses and in males [illegible] mg/kg/day). Thyroid follicular cell adenomas were [illegible] in males and females at both doses; thyroid follic[illegible] carcinomas were increased in females at 100 mg/kg [illegible] increased incidence of thyroid neoplasms appears [illegible]sistent with findings from other HMG-CoA reductase [illegible]tors. These treatment levels represented plasma drug [illegible] (AUC) of approximately 7 and 15 times (males) and [illegible] 25 times (females) the mean human plasma drug [illegible] after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a [illegible] mutagenicity (Ames) test with or without rat [illegible] metabolic activation. In addition, no evidence of [illegible] genetic material was noted in an *in vitro* al[illegible] assay using rat hepatocytes, a V-79 mammalian [illegible] mutation study, an *in vitro* chromosome aberration [illegible] CHO cells, or an *in vivo* chromosomal aberration [illegible] mouse bone marrow.

There was decreased fertility in male rats treated [illegible] vastatin for 34 weeks at 25 mg/kg body weight [illegible] maximum human exposure level, based on AUC, [illegible] receiving 80 mg/day); however, this effect was [illegible] during a subsequent fertility study in which [illegible] was administered at this same dose level to [illegible] weeks (the entire cycle of spermatogenesis [illegible]ymal maturation). No microscopic changes were [illegible] the testes of rats from either study. At 180 [illegible] (which produces exposure levels 22 times higher [illegible] in humans taking 80 mg/day based on surface [illegible] seminiferous tubule degeneration (necrosis and [illegible]matogenic epithelium) was observed. In dogs, [illegible] drug-related testicular atrophy, decreased [illegible] spermatocytic degeneration and giant cell [illegible] mg/kg/day, (approximately 2 times the [illegible] based on AUC, at 80 mg/day). The clinical [illegible] these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been [illegible] Simvastatin was not teratogenic in rats [illegible] up to 10 [illegible] mg/kg/day or in rabbits at doses up to 10 [illegible] doses resulted in 3 times (rat) or 3 times [illegible] exposure based on mg/m² surface area. [illegible] with another structurally-related HMG-CoA [illegible]hibitor, skeletal malformations were ob[illegible] mice.

Rare reports of congenital anomalies have [illegible]lowing intrauterine exposure to HMG-CoA [illegible]tors. In a review*** of approximately 10[illegible]

[illegible] in women exposed to ZOCOR or another [illegible] HMG-CoA reductase inhibitor, the inci[illegible] anomalies, spontaneous abortions and [illegible]ths, did not exceed what would be ex[illegible]al population. The number of cases is ad[illegible]clude a 3- *to 4-fold* increase in congenital [illegible] background incidence. In 89% of the pro[illegible] pregnancies, drug treatment was initi[illegible]nancy and was discontinued at some point [illegible]ster when pregnancy was identified. As [illegible]nt women has not been established and [illegible]rent benefit to therapy with ZOCOR during [illegible]CONTRAINDICATIONS), treatment should [illegible]continued as soon as pregnancy is recog[illegible]ould be administered to women of child[illegible] only when such patients are highly un[illegible] and have been informed of the potential [illegible]

[illegible] whether simvastatin *is excreted in human* [illegible] small amount of another drug in this class [illegible]man milk and because of the potential for [illegible]eactions in nursing *infants,* women taking [illegible]ould not nurse their infants (see CONTRA[illegible]

[illegible]tiveness in pediatric patients have not been [illegible]ecause pediatric patients are not likely to [illegible]holesterol lowering for at least a decade and [illegible]ence with this drug is limited (no studies in [illegible] the age of 20 years), treatment of pediatric [illegible]mvastatin is not recommended at this time.

[illegible]J.M., Freyssinges, C., Ducrocq, M.B., Stephen[illegible]-Postmarketing Surveillance of Lovastatin [illegible]statin Exposure During Pregnancy, *Repro[illegible]xicology*, 10(6):439–446, 1996.

[illegible]REACTIONS

[illegible]rketing controlled clinical studies and their [illegible] (2423 patients with mean duration of fol[illegible]proximately 18 months), 1.4% of patients were [illegible] due to adverse experiences attributable to ZO[illegible]reactions have usually been mild and tran[illegible]ZOCOR has been evaluated for serious adverse reac[illegible] than 21,000 patients and is generally well-[illegible]

[illegible] Experiences

[illegible]eriences occurring at an incidence of 1 percent [illegible] in patients treated with ZOCOR, regardless of [illegible] in controlled clinical studies are shown in the ta[illegible]

	ZOCOR (N = 1583) %	Placebo (N = 157) %	Cholestyramine (N = 179) %
[illegible] Whole			
[illegible] pain	3.2	3.2	8.9
[illegible]	1.6	2.5	1.1
[illegible]inal			
[illegible]ation	2.3	1.3	29.1
[illegible]	1.9	2.5	7.8
[illegible]	1.1	—	4.5
[illegible]	1.9	1.3	14.5
[illegible]	1.3	1.9	10.1
[illegible] System/ [illegible]iatric			
[illegible]	3.5	5.1	4.5
[illegible]			
[illegible] respiratory [illegible]	2.1	1.9	3.4
Musculoskeletal			
Myalgia	1.2	1.3	
Skin			
Eczema	0.8	0.8	
Pruritus	0.5	0.4	
Rash	0.6	0.6	
Special Senses			
Cataract	0.5	0.8	

[illegible] Simvastatin Survival Study

[illegible] Adverse Experiences

[illegible] Scandinavian Simvastatin Survival Study (4S) (see [illegible] PHARMACOLOGY, *Clinical Studies*) involving [illegible] patients treated with 20–40 mg/day of ZOCOR [illegible] or placebo (n=2223), the safety and tolerability [illegible] were comparable between groups over the median [illegible] of the study. The clinical adverse experiences re[illegible] as possibly, probably, or definitely drug-related in [illegible] in either treatment group are shown in the table be[illegible]

	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
[illegible] Whole		
[illegible] pain	0.9	0.9
[illegible]inal		
[illegible]	[illegible]	0.2

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: ~~anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity,~~ fever, chills, ~~flushing, malaise, dyspnea, toxic epidermal necrolysis,~~ erythema multiforme, including Stevens-Johnson ~~syndrome.~~

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilurubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of creatine kinase (CK) levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended. The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR (see NCEP Treatment Guidelines for details on dietary therapy).

The recommended usual starting dose is 20 mg once a day in the evening. Patients who require only a moderate reduction of LDL cholesterol may be started at 10 mg. See below for dosage recommendations for patients receiving concomitant therapy with cyclosporine, fibrates or niacin, and for those with severe renal insufficiency.

The recommended dosing range is 5–80 mg/day as a single dose in the evening. Doses should be individualized according to baseline LDL-C levels, the recommended goal of ther-

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of ZOCOR if cholesterol falls significantly below the targeted range.

Dosage in Patients with Homozygous Familial Hypercholesterolemia

Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

General Recommendations

In the elderly, maximum reductions in LDL cholesterol may be achieved with daily doses of 20 mg of ZOCOR or less.

In patients taking cyclosporine concomitantly with simvastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 5 mg of ZOCOR and should not exceed 10 mg/day.

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of ZOCOR with fibrates or niacin should generally be avoided. However, if ZOCOR is used in combination with fibrates or niacin, the dose of ZOCOR should not exceed 10 mg (see WARNINGS, *Skeletal Muscle*).

Dosage in Patients with Renal Insufficiency

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

HOW SUPPLIED

No. 3588 — Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0726-61 unit of use bottles of 60
(6505-01-354-4549, 5 mg 60's)
NDC 0006-0726-54 unit of use bottles of 90
(6505-01-354-4548, 5 mg 90's)
NDC 0006-0726-28 unit dose packages of 100.

Shown in Product Identification Guide, page 324

No. 3589 — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0735-61 unit of use bottles of 60
(6505-01-354-4545, 10 mg 60's)
NDC 0006-0735-54 unit of use bottles of 90
(6505-01-354-4544, 10 mg 90's)
NDC 0006-0735-28 unit dose packages of 100
(6505-01-354-4543, 10 mg individually sealed 100's)
NDC 0006-0735-82 bottles of 1000
(6505-01-373-7290, 10 mg 1000's)
NDC 0006-0735-87 bottles of 10,000
(6505-01-378-8058, 10 mg 10,000's).

Shown in Product Identification Guide, page 324

No. 3590 — Tablets ZOCOR 20 mg are tan, shield-shaped film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0740-61 unit of use bottles of 60
(6505-01-354-4547, 20 mg 60's)
NDC 0006-0740-28 unit dose packages of 100
NDC 0006-0740-82 bottles of 1000
NDC 0006-0740-87 bottles of 10,000
(6505-01-378-8771, 20 mg 10,000's).

Shown in Product Identification Guide, page 324

No. 3591 — Tablets ZOCOR 40 mg are brick red, shie[illegible] shaped, film-coated tablets, coded MSD 749 on one side a[illegible] ZOCOR on the other. They are supplied as follows:

NDC 0006-0749-61 unit of use bottles of 60
(6505-01-354-4546, 40 mg 60's).

Shown in Product Identification Guide, page 324

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsu[illegible] shaped, film-coated tablets, coded MSD 543 on one side [illegible] 80 on the other. They are supplied as follows:

NDC 0006-0543-61 unit of use bottles of 60.

Shown in Product Identification Guide, page 324

Storage

Store between 5–30°C (41–86°F).

7825430 Issued July 1998

Information on the Merck & Co., Inc. products listed these pages is the full prescribing information from proc

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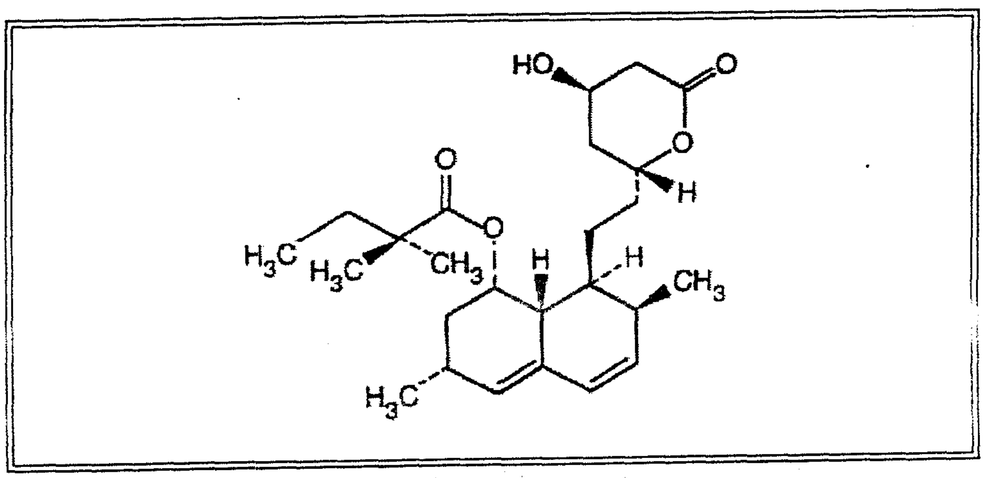
PDR® entry for
Zocor Tablets (Merck)

Description

DESCRIPTION

ZOCOR* (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus* . After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding (beta)-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo- 2 *H* -pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1 *S* -[1(alpha),3(alpha),7(beta),8(beta)(2 *S* *,4 *S* *),-8a(beta)]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

*Registered trademark of MERCK & CO., Inc.

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CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both risk factors for coronary heart disease. Though frequently found in association with low HDL-C, elevated plasma triglycerides (TG) have not been established as an independent risk factor for coronary heart disease (CHD). The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol (total-C) 212-309 mg/dL (5.5-8.0 mmol/L). The patients were followed for a median of 5.4 years. In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR significantly reduced the risk of mortality by 30% (11.5% vs 8.2%, placebo vs ZOCOR); of CHD mortality by 42% (8.5% vs 5.0%); and of having a hospital-verified non-fatal myocardial infarction by 37% (19.6% vs 12.9%). Furthermore, ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (17.2% vs 11.4%) [see CLINICAL PHARMACOLOGY , *Clinical Studies*].

ZOCOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of ZOCOR may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apolipoprotein B (Apo B) also falls substantially during treatment with ZOCOR. As each LDL particle contains one molecule of Apo B, and since in patients with predominant elevations in LDL-C (without accompanying elevation in VLDL) little Apo B is found in other lipoproteins, this strongly suggests that ZOCOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, ZOCOR reduces VLDL and TG and increases HDL-C. The effects of ZOCOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for CHD are unknown.

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding (beta)-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the (beta)-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its (beta)-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the (beta)-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

Clinical Studies

ZOCOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy. Furthermore, improving lipoprotein levels with ZOCOR improved survival in patients with CHD and hypercholesterolemia treated with

20-40 mg per day for a median of 5.4 years.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial or non-familial hypercholesterolemia, ZOCOR given as a single-dose in the evening (the recommended dosing) was similarly effective as when given on a twice-daily basis. ZOCOR consistently and significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio. ZOCOR also decreased TG and increased HDL-C.

The results of 3 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia are presented in TABLE I.

Table I
Dose Response in Patients with Primary Hypercholesterolemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG *
Lower Dose Comparative Study (Mean % Change at Week 6)					
ZOCOR					
5 mg q.p.m.	109	-19	-26	10	-12
10 mg q.p.m.	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study (Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	3
ZOCOR					
20 mg q.p.m.	2221	-28	-38	8	-15
Upper Dose Comparative Study (Mean % Change averaged at Weeks 18 and 24)					
ZOCOR					
40 mg q.p.m.	433	-31	-41	9	-18
80 mg q.p.m.	664	-36	-47	8	-24
* median percent change					

The mean reduction in LDL-C was 47% at the 80-mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG </= 200 mg/dL had a median reduction in TG of 21%, while in 189 patients with TG > 200 mg/dL, the median reduction in TG was 36%. In these studies, patients with TG > 350 mg/dL were excluded.

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of the 12 patients had reductions in LDL-C. In those patients with reductions, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20-40 mg daily (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality (Figure 1) by 30%, (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42%, (p=0.00001, 111 vs 189). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) (Figure 2) by 34%, (p<0.00001, 431 patients vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, (p<0.00001, 252 patients vs 383 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 patients vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. The risk of mortality was significantly decreased in patients >/=60 years of age by 27% and in patients <60 years of age by 37%. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 women vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort.

Figure 1

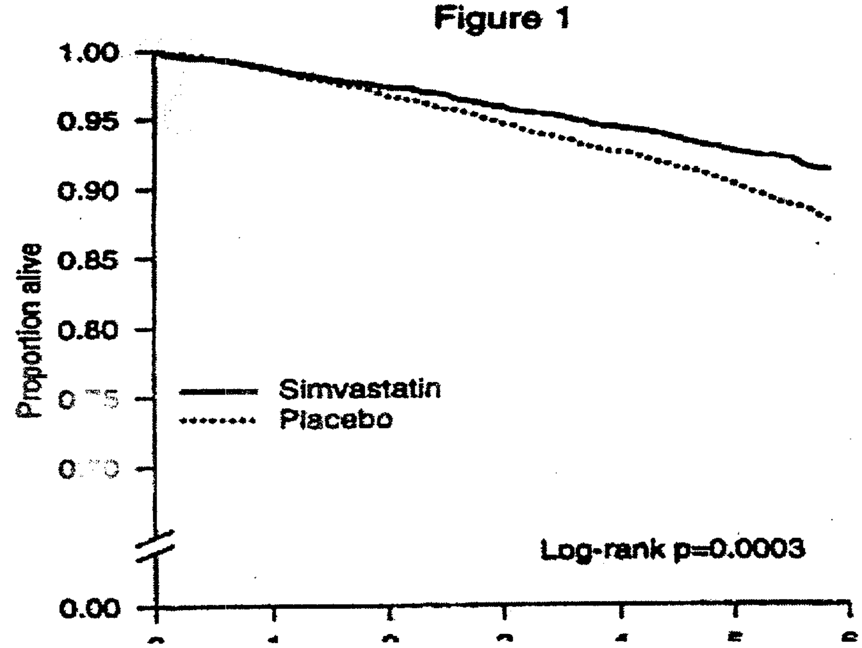
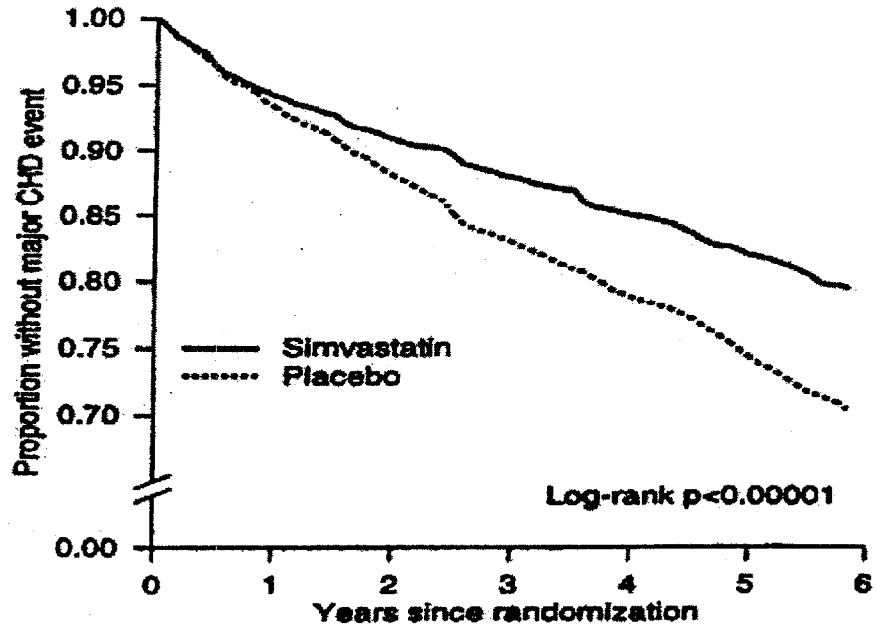


Figure 2



In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled trial, patients with a mean baseline total-C value of 245 mg/dL (6.4 mmol/L) and a mean baseline LDL-C value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. The co-primary endpoints of the trial were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the final angiogram by both these parameters (mean changes in minimum lumen diameter: -0.04 mm with simvastatin vs -0.12 mm with placebo; mean changes in mean lumen diameter: -0.03 mm with simvastatin vs -0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9% simvastatin vs 3.6% placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23% simvastatin vs 33% placebo) and disease regression (18% simvastatin vs 12% placebo). In addition, simvastatin significantly decreased the proportion of patients with new lesions (13% simvastatin vs 24% placebo) and with new total occlusions (5% vs 11%). The mean change per-patient in mean and minimum lumen diameters calculated by comparing angiograms in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).

Figure 3

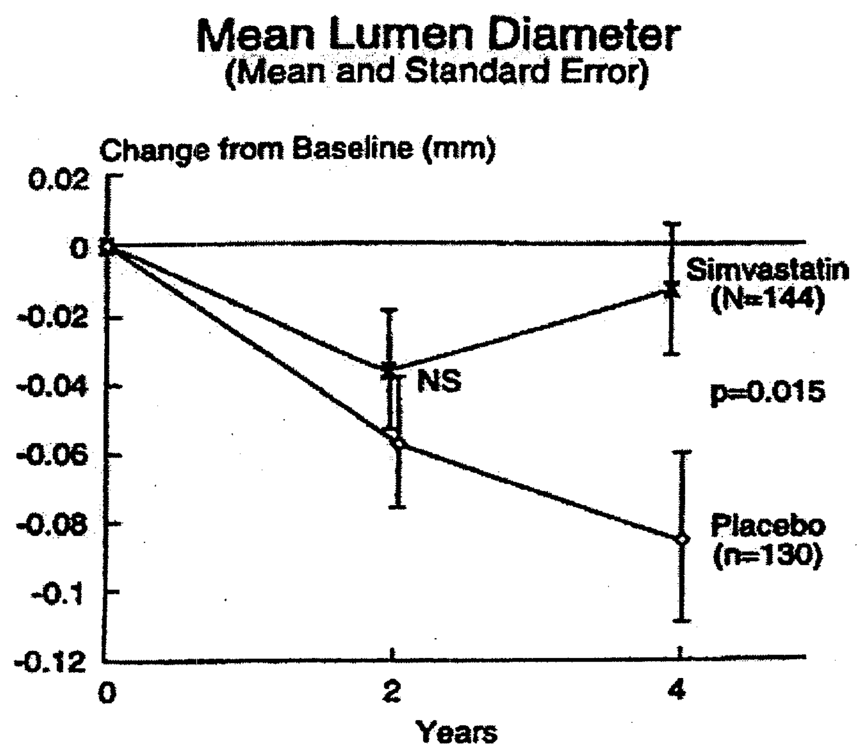
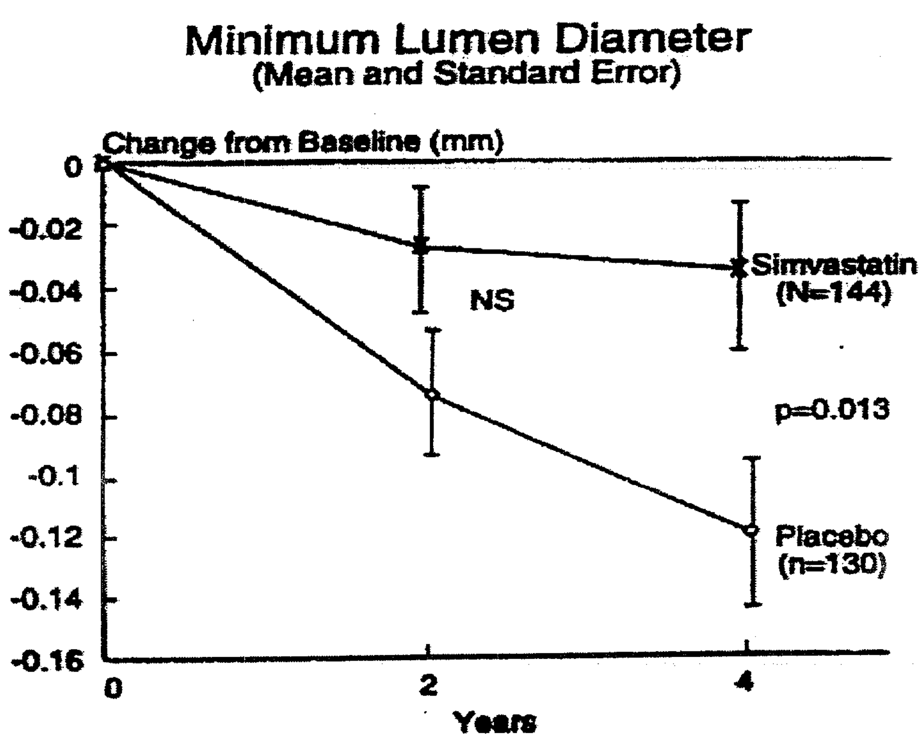


Figure 4



Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin (hCG). In another 24-week study simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg or placebo daily for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

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INDICATIONS AND USAGE

Therapy with lipid-altering agents should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence of coronary heart disease, or other risk factors. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Coronary Heart Disease

In patients with coronary heart disease and hypercholesterolemia, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures.
- Reduce the risk of stroke or transient ischemic attack.

(For a discussion of efficacy results by gender and other predefined subgroups, see CLINICAL PHARMACOLOGY , *Clinical Studies* .)

Hyperlipidemia

ZOCOR is indicated as an adjunct to diet to reduce elevated total-C LDL-C, Apo B, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb**).

ZOCOR is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

General Recommendations

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = total-C - [0.20 × (TG) + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentration should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, ZOCOR is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The NCEP Treatment Guidelines are summarized below:

NCEP Treatment Guidelines LDL-Cholesterol mg/dL (mmol/L)			
Definite Atherosclerotic Disease *	Two or More Other Risk Factors **	Initiation Level	Goal
NO	NO	>/=190 (>/=4.9)	<160 (<4.1)
NO	YES	>/=160 (>/=4.1)	<130 (<3.4)
YES	YES OR NO	>/=130 *** (>/=3.4)	</=100 (</=2.6)
* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).			
** Other risk factors for coronary heart disease (CHD) include: age (males: >/=45 years; females: >/=55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is >/=60 mg/dL (>/=1.6 mmol/L).			
*** In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.			

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is >/= 130 mg/dL (see NCEP Guidelines, above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

ZOCOR is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipoproteinemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons, intermediate-density lipoprotein (IDL), or VLDL (i.e., hyperlipoproteinemia Types I, III, IV, or V).**

** Classification of Hyperlipoproteinemias

	Lipoproteins	Lipid Elevations	
Type	elevated	major	minor
I (rare)	chylomicrons	TG	up->C
IIa	LDL	C	--
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	--
IV	VLDL	TG	up->C
V (rare)	chylomicrons, VLDL	TG	up->C
C = cholesterol, TG = triglycerides, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein, IDL = intermediate-density lipoprotein.			

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as ZOCOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR is contraindicated during pregnancy and in nursing mothers. **ZOCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ZOCOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS , *Pregnancy*).

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WARNINGS

Skeletal Muscle

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (CK) (> 10X the upper limit of normal [ULN]). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely.** In 4S, there was one case of myopathy among 1,399 patients taking simvastatin 20 mg and no cases among 822 patients taking 40 mg daily for a median duration of 5.4 years. In two 6-month controlled clinical studies, there was one case of myopathy among 436 patients taking 40 mg and 5 cases among 669 patients taking 80 mg. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the designs of these studies (see below).

Myopathy caused by drug interactions.

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (>/= 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, and the antidepressant nefazodone.

Reducing the risk of myopathy.

1. **General measures. Patients starting therapy with simvastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness.** A CK level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. **Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.
   Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.
2. **Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS , *Drug Interactions*). Physicians contemplating combined therapy with**

simvastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. If one of these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg (see DOSAGE AND ADMINISTRATION, *General Recommendations* and *Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Interruption of simvastatin therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

Liver Dysfunction

Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL PHARMACOLOGY , *Clinical Studies*), the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and periodically thereafter (e.g., semiannually) for the first year of treatment or until one year after the last elevation in dose. Patients titrated to the 80-mg dose should receive an additional test at 3 months. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

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PRECAUTIONS

General

Simvastatin may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness (see WARNINGS , *Skeletal Muscle*).

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Drug Interactions

Cyclosporine, Itraconazole, Ketoconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin, Clarithromycin, HIV protease inhibitors, Nefazodone (see WARNINGS , *Skeletal Muscle*).

Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolized by the cytochrome P-450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform (see WARNINGS , *Skeletal Muscle*).

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review*** of approximately 100 prospectively followed pregnancies in women exposed to ZOCOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with ZOCOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ZOCOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with simvastatin is not recommended at this time.

***Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology* , 10(6):439-446, 1996.

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ADVERSE REACTIONS

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well-tolerated.

Clinical Adverse Experiences

Adverse experiences occurring at an incidence of 1 percent or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

Adverse Experiences in Clinical Studies Incidence 1 Percent or Greater, Regardless of Causality			
	ZOCOR (N = 1,583) %	Placebo (N = 157) %	Cholestyramine (N = 179) %
Body as a Whole			
Abdominal pain	3.2	3.2	8.9
Asthenia	1.6	2.5	1.1
Gastrointestinal			
Constipation	2.3	1.3	29.1
Diarrhea	1.9	2.5	7.8
Dyspepsia	1.1	--	4.5
Flatulence	1.9	1.3	14.5
Nausea	1.3	1.9	10.1
Nervous System/Psychiatric			
Headache	3.5	5.1	4.5
Respiratory			
Upper respiratory infection	2.1	1.9	3.4

Scandinavian Simvastatin Survival Study
Clinical Adverse Experiences

In 4S (see CLINICAL PHARMACOLOGY , *Clinical Studies*) involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in >/=0.5% in either treatment group are shown in the table below:

Drug-Related Clinical Adverse Experiences in 4S Incidence 0.5 Percent or Greater		
	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
Body as a Whole		
Abdominal pain	0.9	0.9
Gastrointestinal		
Diarrhea	0.5	0.3
Dyspepsia	0.6	0.5
Flatulence	0.9	0.7
Nausea	0.4	0.6

Musculoskeletal		
Myalgia	1.2	1.3
Skin		
Eczema	0.8	0.8
Pruritus	0.5	0.4
Rash	0.6	0.6
Special Senses		
Cataract	0.5	0.8

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, (gamma)-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS , *Liver Dysfunction*). About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS , *Skeletal Muscle*).

Concomitant Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS , *Skeletal Muscle*).

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OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

The dialyzability of simvastatin and its metabolites in man is not known at present.

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DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR (see NCEP Treatment Guidelines for details on dietary therapy).

The recommended usual starting dose is 20 mg once a day in the evening. Patients who require only a moderate reduction of LDL-C may be started at 10 mg. See below for dosage recommendations for patients receiving concomitant therapy with cyclosporine, fibrates or niacin, and for those with severe renal insufficiency.

The recommended dosing range is 5-80 mg/day as a single dose in the evening. Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy (see NCEP Treatment Guidelines) and the patient's response. Adjustments of dosage should be made at intervals of 4 weeks or more.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of ZOCOR if cholesterol falls significantly below the targeted range.

Dosage in Patients with Homozygous Familial Hypercholesterolemia

Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

General Recommendations

In the elderly, maximum reductions in LDL-C may be achieved with daily doses of 20 mg of ZOCOR or less.

In patients taking cyclosporine concomitantly with simvastatin (see WARNINGS , *Skeletal Muscle*), therapy should begin with 5 mg of ZOCOR and should not exceed 10 mg/day.

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of ZOCOR with fibrates or niacin should generally be avoided. However, if ZOCOR is used in combination with fibrates or niacin, the dose of ZOCOR should not exceed 10 mg (see WARNINGS , *Skeletal Muscle*).

Dosage in Patients with Renal Insufficiency

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY , *Pharmacokinetics* and WARNINGS , *Skeletal Muscle*).

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HOW SUPPLIED

No. 3588 -- Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0726-61 unit of use bottles of 60

(6505-01-354-4549, 5 mg 60's)

NDC 0006-0726-54 unit of use bottles of 90

(6505-01-354-4548, 5 mg 90's)

NDC 0006-0726-28 unit dose packages of 100.

No. 3589 -- Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0735-61 unit of use bottles of 60

(6505-01-354-4545, 10 mg 60's)

NDC 0006-0735-54 unit of use bottles of 90

(6505-01-354-4544, 10 mg 90's)

NDC 0006-0735-28 unit dose packages of 100

(6505-01-354-4543, 10 mg individually sealed 100's)

NDC 0006-0735-82 bottles of 1000

(6505-01-373-7290, 10 mg 1000's)

NDC 0006-0735-87 bottles of 10,000

(6505-01-378-8058, 10 mg 10,000's).

No. 3590 -- Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0740-61 unit of use bottles of 60

(6505-01-354-4547, 20 mg 60's)

NDC 0006-0740-28 unit dose packages of 100

NDC 0006-0740-82 bottles of 1000

NDC 0006-0740-87 bottles of 10,000

(6505-01-378-8771, 20 mg 10,000's).

No. 3591 -- Tablets ZOCOR 40 mg are brick red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0749-61 unit of use bottles of 60

(6505-01-354-4546, 40 mg 60's).

No. 6577 -- Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:

NDC 0006-0543-61 unit of use bottles of 60.

Storage

Store between 5-30°C (41-86°F).

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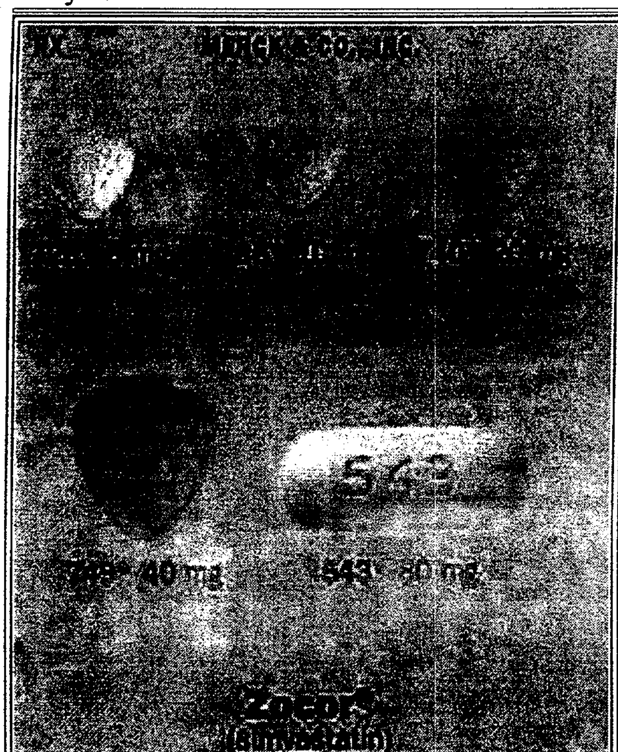

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